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A 4-year-old boy is brought to the emergency department for difficulty breathing and a productive cough. He has a past medical history of recurrent episodes of sinusitis and otitis media. The respiratory infections typically have a protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th intercostal space. Which of the following is most likely to be dysfunctional in this patient?

A. C1 complement component
B. Chloride channels
C. Dynein arms
D. IL-2 receptors
E. Immunoglobulin gene rearrangement
F. NADPH oxidase

Submit

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A 4-year-old boy is brought to the emergency department for difficulty breathing and a productive cough. He has a past medical history of recurrent episodes of sinusitis and otitis media. The respiratory infections typically have a protracted course but respond to high-dose antibiotic therapy. Pulmonary auscultation shows crackles and wheezing. Cardiovascular examination shows a cardiac point of maximal impulse that is palpated at the right 5th intercostal space. Which of the following is most likely to be dysfunctional in this patient?

A. C1 complement component (2%)
B. Chloride channels (10%)
✓ C. Dynein arms (72%)
D. IL-2 receptors (2%)
E. Immunoglobulin gene rearrangement (4%)
F. NADPH oxidase (7%)

Correct

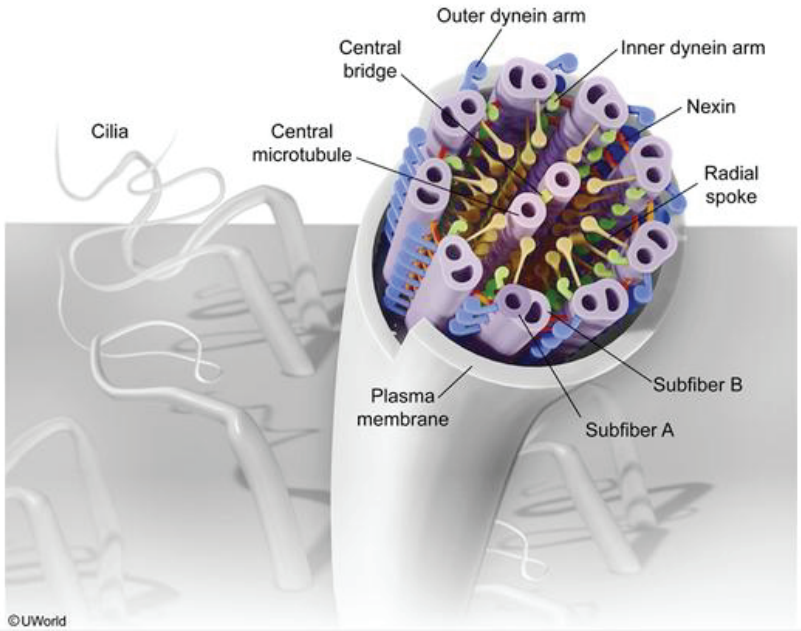
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Exhibit Display

Cilium structure



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This patient's history of recurrent respiratory infections and dextrocardia on physical examination are suggestive of **Kartagener syndrome**, a form of **primary ciliary dyskinesia** (PCD). This autosomal recessive condition is caused by a wide variety of mutations that impair ciliary structure or function.

Eukaryotic flagella and cilia are composed of a central core known as the axoneme that is surrounded by cell membrane. The axoneme of flagella and motile cilia consists of a circular array of microtubule doublets surrounding 2 central microtubules (9+2 arrangement); the axoneme is anchored to the cell by a basal body. Each doublet has an A and B subunit and is connected to the adjacent doublet via dynein arms. These dynein arms contain an ATPase that generates energy to slide the microtubules past each other, producing ciliary movement. Primary ciliary dyskinesia can result from failure of the **dynein arms** to develop normally.

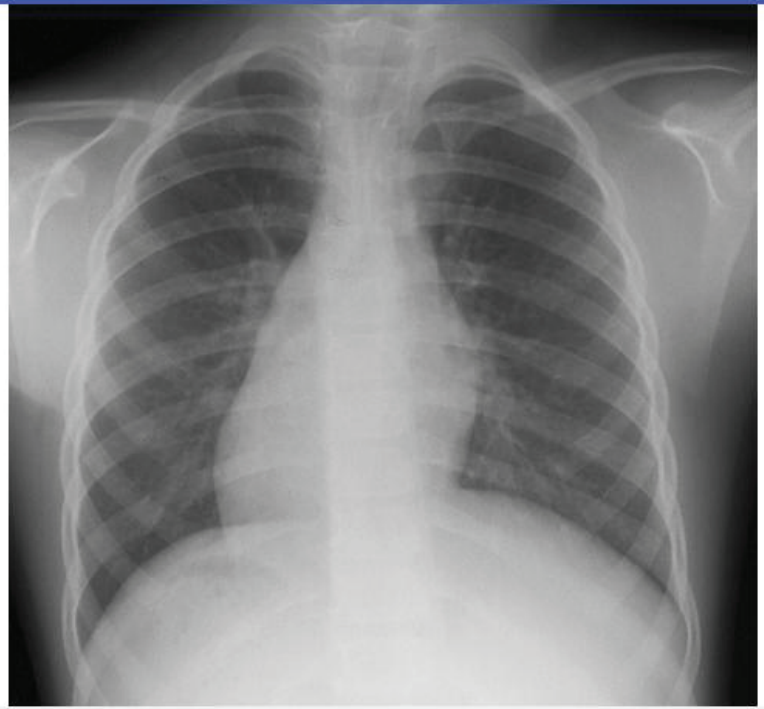
Patients with PCD experience **recurrent respiratory infections** (eg, chronic sinusitis, bronchiectasis) as a result of impaired mucociliary clearance. In addition, impaired ciliary movement during embryogenesis can cause **situs inversus** (reversed right/left positioning of internal organs). **Infertility** in men (impaired sperm motility) and women (immobility of fallopian tube cilia) is another frequent manifestation.

(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated

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(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated

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(Choice A) Deficiency of the C1 complement component causes increased susceptibility to encapsulated bacteria (eg, *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) and also predisposes to developing systemic lupus erythematosus.

(Choice B) Epithelial cell chloride channels are defective in cystic fibrosis. Although patients with cystic fibrosis typically have recurrent respiratory infections and infertility, dextrocardia/situs inversus are not seen.

(Choice D) Defects in T-cell IL-2 receptors can cause severe combined immunodeficiency disease (SCID).

(Choice E) Immunoglobulin gene rearrangement is impaired in hyper-IgM syndrome. In this disorder, B cells produce high amounts of IgM but are unable to switch production to other immunoglobulin classes.

(Choice F) NADPH oxidase deficiency causes chronic granulomatous disease.

Educational objective:
Kartagener syndrome is a form of primary ciliary dyskinesia characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis. It occurs due to mutations that impair the structure or function of cilia. Cystic fibrosis also causes chronic respiratory infections, but it is not associated with situs inversus.

Immunology Pathology (General Principles) Immotile cilia syndrome

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An 18-year-old man is evaluated due to 3 months of lower extremity pain. The pain is persistent and present both day and night. He has no fever, chills, or history of leg trauma. Imaging shows an expansile lesion of the distal femur. Surgical resection is performed, and the specimen is shown below.



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Mutations involving which of the following genes are most likely present in this patient?

- A. *BRAF*
- B. *HER2*
- C. *KRAS*
- D. *RB1*
- E. *RET*

Submit

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Mutations involving which of the following genes are most likely present in this patient?

- A. *BRAF* (9%)
- B. *HER2* (0%)
- C. *KRAS* (9%)
- ✓ D. *RB1* (71%)
- E. *RET* (8%)

Correct

71%

26 secs

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Proto-oncogenes 1-hit GAIN of function		Tumor suppressor genes 2-hit LOSS of function	
RAS (GTP-binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	• Breast & ovarian cancer
MYC (Transcription factor)	• Burkitt lymphoma	***APC/β-catenin*** (Wnt signaling pathway)	• Colon, gastric & pancreatic cancer • Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	***TP53*** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma

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ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	• Chronic myelogenous leukemia	***WT1*** (Urogenital differentiation)	• Wilms tumor
BRAF (Ras signal transduction)	• Hairy cell leukemia • Melanoma	***VHL*** (Ubiquitin ligase component)	• Renal cell carcinoma • Von Hippel-Lindau syndrome

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This patient's expansile tumor in the distal femur likely indicates **osteosarcoma**, the most common primary bone tumor affecting children and **young adults**. Most cases arise at the metaphysis of long bones and present with progressive pain and swelling.

Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression.

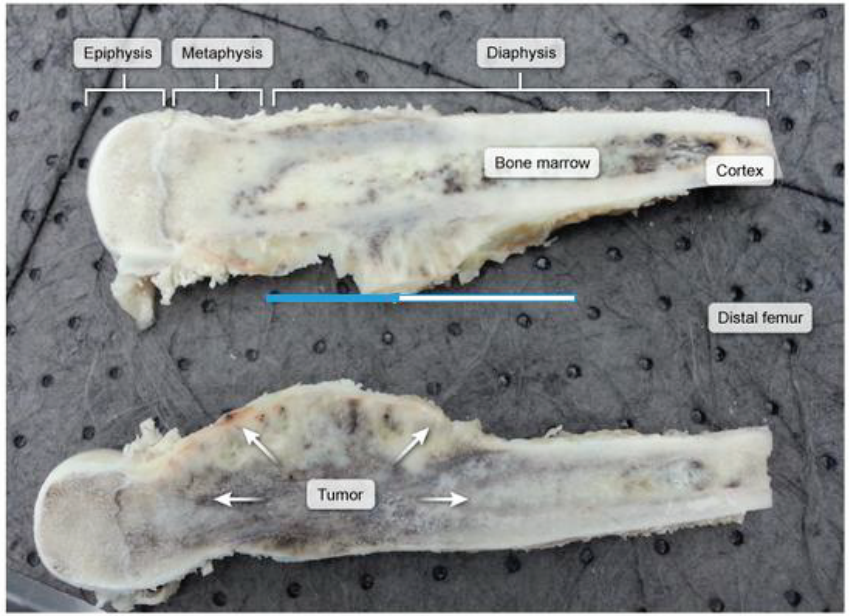
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ERBB2

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Osteosarcoma



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Osteosarcomas typically form when a **mesenchymal stem cell** develops mutations in the following genes:

- ***RB1*** tumor suppressor gene, which encodes for RB, a protein that regulates cell-cycle progression. Inactivating mutations to *RB1* promote unchecked and unregulated cellular replication and are associated with osteosarcoma, **retinoblastoma**, melanoma, and soft-tissue sarcomas.
- *TP53* tumor suppressor gene, which encodes for P53, a protein that regulates cell-cycle progression and maintains genomic integrity by activating DNA repair following damage. Germ-line mutations to *TP53* are associated with **Li-Fraumeni syndrome**, which increases the risk for multiple tumors (eg, osteosarcoma, other bone and soft-tissue sarcomas, breast cancer, brain tumors, adrenal carcinomas).

(Choice A) Activating mutations of *BRAF* are responsible for most cases of hairy cell leukemia, a B-cell neoplasm that typically presents in older patients with pancytopenia, splenomegaly, and systemic symptoms (eg, fatigue, recurrent infections). It is also present in many cases of malignant melanoma.

(Choice B) *HER2*, an oncogene encoding for an epidermal growth factor receptor, is amplified or overexpressed in many forms of invasive breast cancer. Treatment of the *HER2* gene product can improve outcomes in these individuals.

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overexpressed in many forms of invasive breast cancer. Treatment of the *HER2* gene product can improve outcomes in these individuals.

(Choice C) Activating mutations in the *KRAS* proto-oncogene are common in colorectal cancer and non-small cell lung cancer. *KRAS* encodes for a GTPase that relays cellular growth and proliferation signals from outside the cell.

(Choice E) Germ-line mutations of the *RET* proto-oncogene cause multiple endocrine neoplasia type 2, which is associated with pheochromocytoma, medullary thyroid cancer, parathyroid hyperplasia, and/or mucosal neuromas.

Educational objective:

Osteosarcoma is the most common primary bone malignancy in children and young adults. It occurs most frequently at the metaphyses of long bones and presents with local pain and swelling. Most cases are associated with sporadic or inherited mutations in *RB1* (hereditary retinoblastoma) and *TP53* (Li-Fraumeni syndrome).

References

- Understanding the osteosarcoma pathobiology: a comparative oncology approach.

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A 32-year-old chef accidentally slices into the tip of her thumb while hurriedly trimming ribeye steaks with a knife. The laceration extends through the skin into the subcutaneous pulp. Which of the following sequences is most likely to occur in the subsequent wound healing process?

A. Angiogenesis → cellular infiltration → fibrin clot formation
B. Angiogenesis → fibrin clot formation → cellular infiltration
C. Cellular infiltration → angiogenesis → fibrin clot formation
D. Cellular infiltration → fibrin clot formation → angiogenesis
E. Fibrin clot formation → angiogenesis → cellular infiltration
F. Fibrin clot formation → cellular infiltration → angiogenesis

Submit

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A 32-year-old chef accidentally slices into the tip of her thumb while hurriedly trimming ribeye steaks with a knife. The laceration extends through the skin into the subcutaneous pulp. Which of the following sequences is most likely to occur in the subsequent wound healing process?

A. ~~Angiogenesis → cellular infiltration → fibrin clot formation~~ (1%)

B. ~~Angiogenesis → fibrin clot formation → cellular infiltration~~ (0%)

C. ~~Cellular infiltration → angiogenesis → fibrin clot formation~~ (4%)

D. ~~Cellular infiltration → fibrin clot formation → angiogenesis~~ (21%)

E. Fibrin clot formation → angiogenesis → cellular infiltration (3%)

✓ F. Fibrin clot formation → cellular infiltration → angiogenesis (68%)

Correct

68%
Answered correctly

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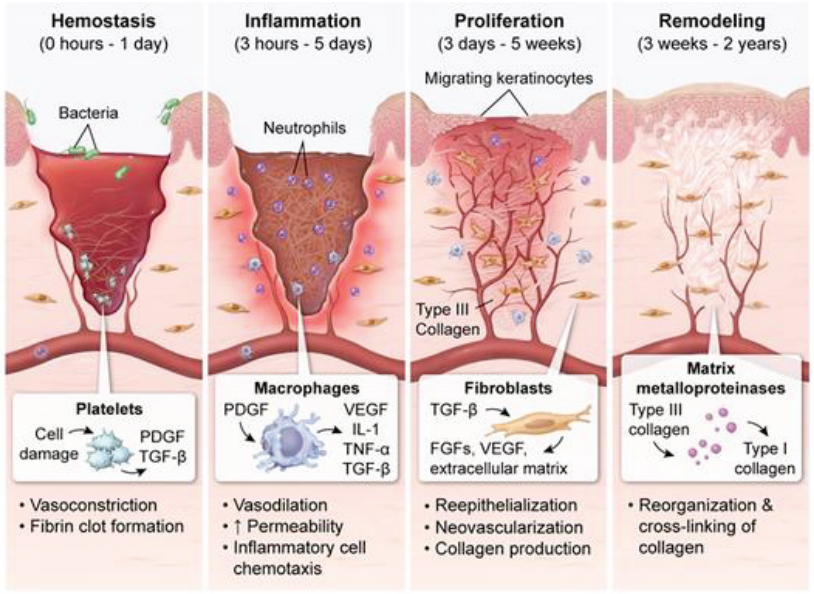
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Phases of wound healing



FGF = fibroblast growth factor; **PDGF** = platelet-derived growth factor;
TGF-β = transforming growth factor-beta; **VEGF** = vascular endothelial growth factor.

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TGF-β = transforming growth factor-beta; VEGF = vascular endothelial growth factor.

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Acute **wounds**, such as the sharp laceration this patient sustained from a knife, transition through an organized **healing process** to restore continuity and tensile strength. This process involves activation and recruitment of different cell types during 4 sequential (but overlapping) phases: hemostasis, inflammation, proliferation, and maturation.

Hemostasis, which occurs immediately after tissue injury, involves small vessel constriction, **platelet aggregation**, and clotting cascade activation that leads to platelet plugging, fibrin clot formation, and cessation of bleeding. For relatively minor injuries, hemostasis is often accomplished within minutes. The fibrin clot that is formed during this phase provides a scaffold for subsequent wound healing.

Inflammation usually starts within hours of injury. During this phase, mast cells degranulate, releasing histamine and other chemical mediators that increase vascular permeability and promote **cellular infiltration** (eg, neutrophils, monocytes). Neutrophils digest bacteria, necrotic tissue, and foreign debris. Monocytes are transformed into macrophages, which secrete growth factors (eg, transforming growth factor-beta, vascular endothelial growth factor) that promote the next phase of healing.

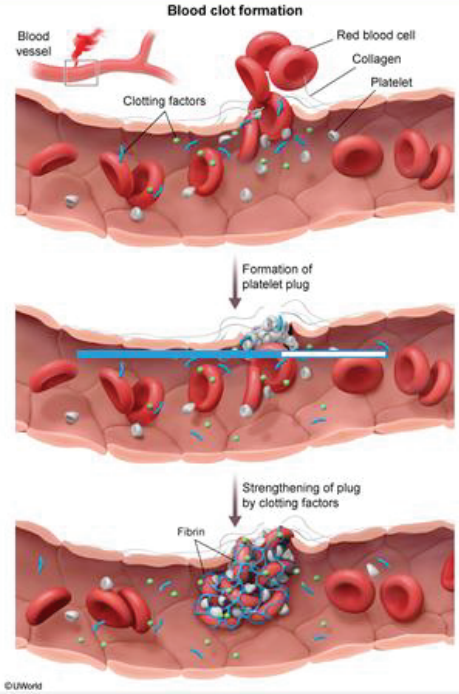
Proliferation, which begins during the inflammatory phase and continues for weeks afterward, leads to replacement of injured or missing tissue via the following:

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TGF-β = transforming growth factor-beta; VEGF = vascular endothelial growth factor

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Proliferation, which begins during the inflammatory phase and continues for weeks afterward, leads to replacement of injured or missing tissue via the following:

- **Epithelization:** Basal keratinocyte proliferation and migration of new epithelial cells form a new superficial epithelial layer that acts as a barrier to bacteria.
- **Fibroplasia:** Fibroblasts proliferate and synthesize ground substance and collagen, forming a matrix into which capillaries can grow. Simultaneous contraction of myofibroblasts (ie, differentiated fibroblasts that produce contractile proteins) helps decrease the wound size.
- **Angiogenesis:** Proliferation and migration of endothelial cells from nearby blood vessels lead to ingrowth of new capillaries into the collagen matrix.

Maturation, the final phase of wound healing, results in **collagen remodeling and cross-linking**, which are the primary mechanisms by which the tensile strength of the wound increases.

Educational objective:
Wounds typically heal according to an organized sequence of 4 phases: hemostasis (fibrin clot formation), inflammation (cellular infiltration), proliferation (reepithelization, fibroplasia, and angiogenesis), and maturation (collagen remodeling).

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A 62-year-old man is evaluated for worsening cough, shortness of breath, and episodic hemoptysis over the past 6 months. The patient has also had a 15-kg (33-lb) weight loss over the same period without any change in his diet or activity level. He has a 50-pack-year smoking history and does not use alcohol or illicit drugs. BMI is 18 kg/m^2. The patient appears cachectic with temporal wasting and generalized loss of muscle mass. Chest x-ray reveals a large lung mass with mediastinal lymphadenopathy and pleural effusion. Which of the following cellular processes is most likely responsible for this patient's muscle loss?

A. Covalent attachment of ubiquitin to muscle proteins
B. Plasma membrane rupture with leakage of cellular contents
C. Plasma membrane instability due to defective dystrophin
D. Progressive shortening of chromosomal telomeres
E. Reprogramming of undifferentiated mesenchymal cells

Submit

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A 62-year-old man is evaluated for worsening cough, shortness of breath, and episodic hemoptysis over the past 6 months. The patient has also had a 15-kg (33-lb) weight loss over the same period without any change in his diet or activity level. He has a 50-pack-year smoking history and does not use alcohol or illicit drugs. BMI is 18 kg/m^2. The patient appears cachectic with temporal wasting and generalized loss of muscle mass. Chest x-ray reveals a large lung mass with mediastinal lymphadenopathy and pleural effusion. Which of the following cellular processes is most likely responsible for this patient's muscle loss?

- ✓ A. Covalent attachment of ubiquitin to muscle proteins (62%)
- B. ~~Plasma membrane rupture with leakage of cellular contents~~ (19%)
- C. ~~Plasma membrane instability due to defective dystrophin~~ (2%)
- D. ~~Progressive shortening of chromosomal telomeres~~ (5%)
- E. Reprogramming of undifferentiated mesenchymal cells (8%)

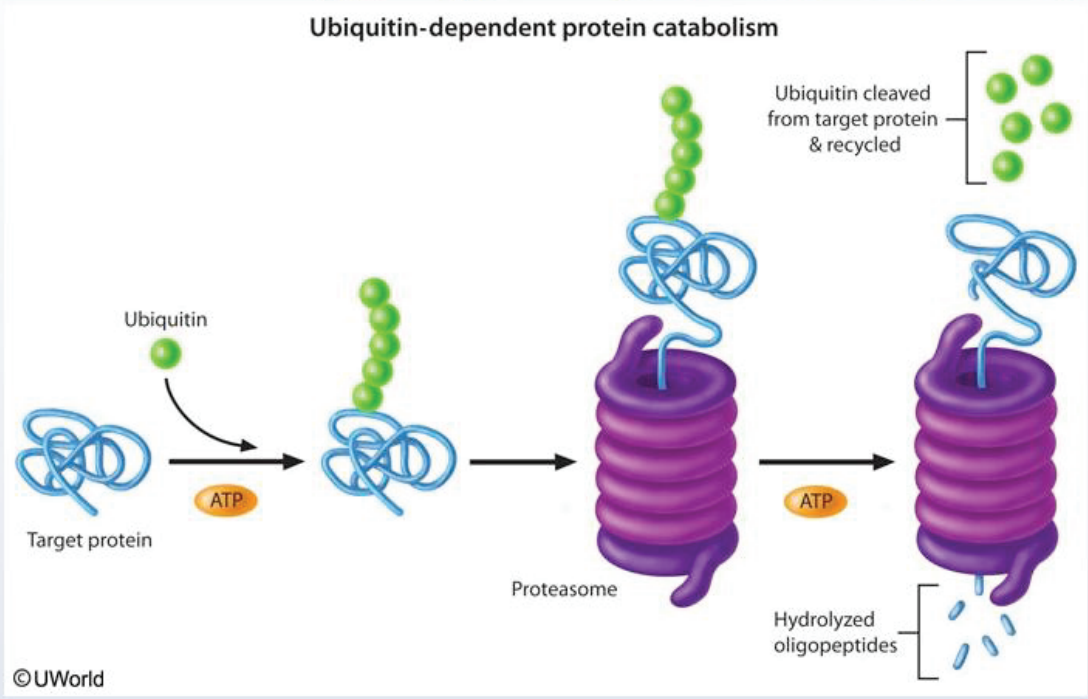
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This patient who has a 50-pack-year smoking history and a mediastinal mass likely has muscle atrophy due to cancer-related **cachexia**. Cachexia is a hypermetabolic state driven by elevated pro-inflammatory cytokines (eg, tumor necrosis factor-alpha, interleukin-6), which stimulate the **ubiquitin-proteasome**

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This patient who has a 50-pack-year smoking history and a mediastinal mass likely has muscle atrophy due to cancer-related **cachexia**. Cachexia is a hypermetabolic state driven by elevated pro-inflammatory cytokines (eg, tumor necrosis factor-alpha, interleukin-6), which stimulate the **ubiquitin-proteasome pathway** to degrade skeletal muscle proteins (eg, actin, myosin).

The ubiquitin-proteasome pathway is the major eukaryotic mechanism for **selective proteolysis** (the destruction of targeted proteins). The addition of ubiquitin multimers to a target protein marks it for **rapid** destruction by the proteasome, whereby the protein is unfolded within the proteasome core and chopped into small oligopeptides. These oligopeptides can be further degraded by cytosolic peptidases into individual amino acids.

Other proteolytic pathways play a less prominent role in the degradation of muscle tissue. Lysosomes, membrane-bound organelles that contain proteases and other digestive enzymes, are primarily tasked with breaking down extracellular components that are brought into the cell via endocytosis and with slowly recycling obsolete cytosolic organelles and debris.

(Choice B) Necrosis is characterized by cellular injury and premature death due to external factors such as infection, toxin, or trauma. It is often characterized by irreparable damage to the cellular membrane with subsequent leakage of cellular contents.

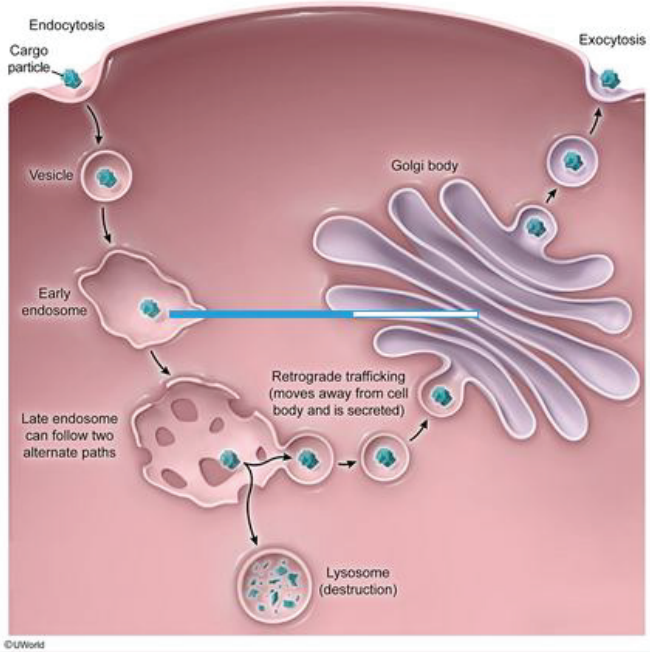
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This patient who has a 50 pack-year smoking history and a mediastinal mass likely has muscle atrophy

Exhibit Display

Endosomal pathway



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subsequent leakage of cellular contents.

(Choice C) Both Duchenne and Becker muscular dystrophies are caused by X-linked mutations to the dystrophin gene. Dystrophin provides mechanical stability to muscle cells during contraction. Mutations are associated with membrane tears that allow calcium to enter the cell and cause myofiber damage.

(Choice D) Telomeres are DNA-protein structures at the end of chromosomes that shorten with each cell division. When telomeres shorten beyond a certain point, the cell undergoes apoptosis or senescence.

(Choice E) Reprogramming of undifferentiated mesenchymal cells (eg, connective tissue) is a form of metaplasia. Metaplasia is characterized by the substitution of one differentiated cell type for another differentiated cell type not normally found in that tissue (eg, bone formation in muscle tissue after muscle injury).

Educational objective:

The ubiquitin-proteasome pathway mediates targeted protein degradation, which allows for rapid disposal of unneeded intracellular proteins. In cancer-related cachexia, high levels of pro-inflammatory cytokines lead to increased ubiquitination of sarcomeric muscle proteins, which in turn leads to extensive skeletal muscle loss.

References

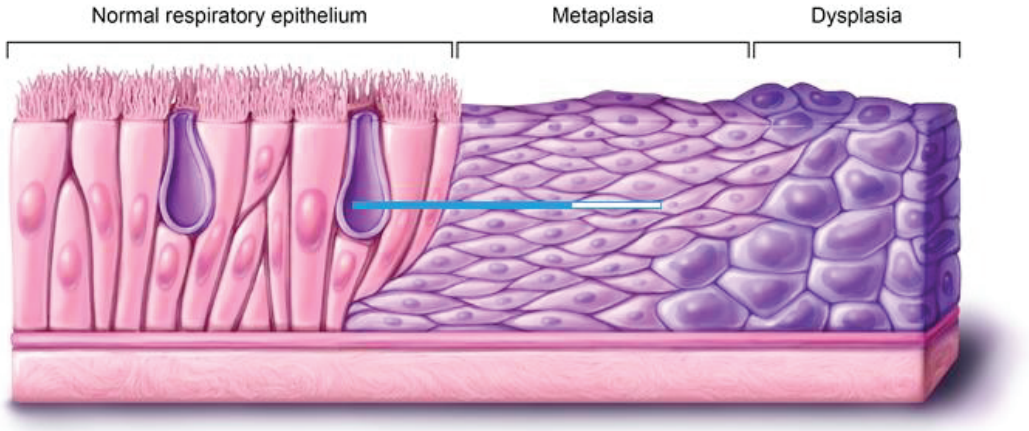
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subsequent leakage of colonic contents.

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Squamous metaplasia



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A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

A. Epidermal growth factor
B. Fibroblast growth factor
C. Insulin-like growth factor 1
D. Interferon-γ
E. Interleukin-1

Submit

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A 34-year-old woman comes to the office due to vague abdominal pain over the past several months. She has no significant past medical history. The patient does not use tobacco or alcohol. Temperature is 36.7 C (98.1 F). On physical examination, right upper quadrant fullness is present. Abdominal imaging reveals a dense liver mass. Angiography shows a well-demarcated, highly vascularized tumor surrounded by normal liver parenchyma. Which of the following substances most likely contributed the most to blood vessel development in this patient's tumor?

A. ~~Epidermal growth factor~~ (34%)
✓ B. Fibroblast growth factor (53%)
C. Insulin-like growth factor 1 (9%)
D. ~~Interferon-γ~~ (1%)
E. ~~Interleukin-1~~ (1%)

Correct

53%
Answered correctly

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This patient has a highly vascularized liver tumor, possibly a benign hepatic hemangioma. Many cases are discovered incidentally. **Angiogenesis** (blood vessel formation) is predominantly driven by the following 2 substances:

- **Vascular endothelial growth factor** (VEGF): VEGF stimulates angiogenesis in a variety of tissues (normal, chronically inflamed, healing, or neoplastic). As VEGF increases endothelial cell motility and proliferation, new capillaries begin to sprout.
- **Fibroblast growth factor** (FGF): FGF-2 is produced by a wide range of cells and is involved in endothelial cell proliferation, migration, and differentiation. FGF-2 also appears to play an important role in embryogenesis by stimulating angioblast production. As a group, FGFs not only contribute to angiogenesis, but also to embryonic development, hematopoiesis, and wound repair (by recruiting macrophages, fibroblasts, and endothelial cells to damaged tissues).

However, the laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

(Choice A) Epidermal growth factor (EGF), not to be confused with VEGF, has a mitogenic influence on epithelial cells, hepatocytes, and fibroblasts. EGF does not appear to play as important a role in angiogenesis as VEGF or FGF-2.

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(Choice C) Insulin-like growth factor 1 (IGF-1), or somatomedin C, is synthesized predominantly by growth hormone-influenced hepatocytes and serves to stimulate cell growth and multiplication. IGF-1 does not appear to directly stimulate angiogenesis, but it can indirectly promote it by encouraging cell growth.

(Choices D and E) Although the proinflammatory nature of interleukin-1 (IL-1) can induce the release of other proinflammatory cytokines that trigger cellular VEGF expression, IL-1 does not appear to directly stimulate angiogenesis. Similarly, although interferon-γ can indirectly promote neovascularization through activation of macrophages (can release VEGF), it does not appear to directly stimulate angiogenesis.

Educational objective:
The key growth factors that promote angiogenesis in neoplastic and granulation tissue are vascular endothelial growth factor (VEGF) and fibroblast growth factor. Proinflammatory cytokines (eg, interleukin-1, interferon-γ) can indirectly promote angiogenesis through increased VEGF expression. The laminin in basement membranes may pose a physical barrier to the sprouting of new blood vessels.

Pathology	Pathology (General Principles)	Hemangioma
Subject	System	Topic

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A 65-year-old woman is being evaluated following an episode of syncope that occurred after prolonged standing. She used to exercise in the local gym but has become easily fatigued recently. The patient has had occasional dark stools. She has lost 5 kg (11 lb) in the past few weeks due to "poor appetite." She does not smoke, drink alcohol, or use illicit drugs. Family history is negative for cancers. Vital signs reveal mild orthostatic hypotension. Physical examination is unremarkable, but stool is positive for occult blood. Colonoscopy reveals 2 polyps. The pathology report shows advanced adenomatous changes in one polyp and adenocarcinoma in the other. A mutation in which of the following genes is most likely responsible for the transformation from advanced adenoma to adenocarcinoma in this patient?

- A. *BRCA1*
- B. *CCND1*
- C. *KRAS*
- D. *NMYC*
- E. *TP53*
- F. *WT1*

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had occasional dark stools. She has lost 5 kg (11 lb) in the past few weeks due to "poor appetite." She does not smoke, drink alcohol, or use illicit drugs. Family history is negative for cancers. Vital signs reveal mild orthostatic hypotension. Physical examination is unremarkable, but stool is positive for occult blood. Colonoscopy reveals 2 polyps. The pathology report shows advanced adenomatous changes in one polyp and adenocarcinoma in the other. A mutation in which of the following genes is most likely responsible for the transformation from advanced adenoma to adenocarcinoma in this patient?

- A. *BRCA1* (1%)
- B. *CCND1* (2%)
- C. *KRAS* (31%)
- D. *NMYC* (1%)
- ✓ E. *TP53* (62%)
- F. *WT1* (0%)

Correct

62%
Answered correctly

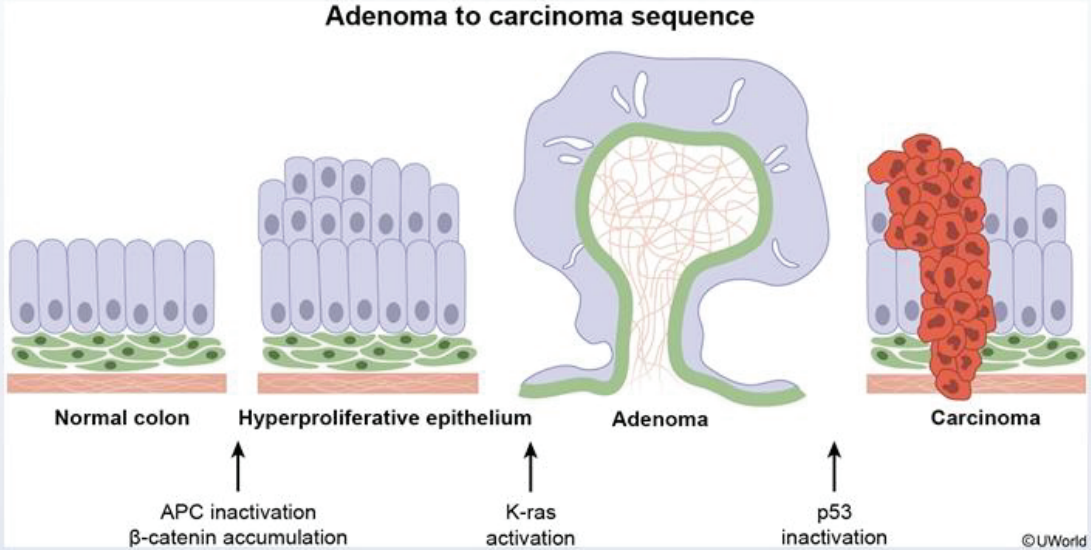
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Explanation



Colon cancer is one of the most common malignancies in the United States. Its incidence increases with age, and it affects men and women equally. A diet high in fat and carbohydrates and low in fiber increases the risk. Certain diseases (eg, inflammatory bowel disease) and genetic factors also play an important role.

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Colon cancer is one of the most common malignancies in the United States. Its incidence increases with age, and it affects men and women equally. A diet high in fat and carbohydrates and low in fiber increases the risk. Certain diseases (eg, inflammatory bowel disease) and genetic factors also play an important role.

Most cases of **sporadic** colon adenocarcinoma arise from preexisting adenomatous **polyps**. The transformation of normal mucosal cells into malignant ones is caused by a series of gene mutations, the **adenoma to carcinoma sequence**:

1. **Progression from normal mucosa to a small adenomatous polyp (adenoma)**. The initial appearance of small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene. *APC* is located on chromosome 5, and its mutation leads to β-catenin accumulation and uncontrolled cell proliferation.
2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step by leading to a protein that also stimulates unregulated cell growth.
3. **Malignant transformation** of adenoma into carcinoma requires mutation of *TP53*.

Sometimes called a "molecular policeman," ***TP53*** is an antioncogene (**tumor suppressor gene**) that codes for protein p53, which triggers apoptosis of cells with damaged DNA. A *TP53* mutation allows cells with genomic errors to enter the cell cycle. Such a mutation is considered the last "**hit**" in the adenoma to carcinoma sequence (mutations are found in most colon carcinomas but rarely in adenomas).

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carcinoma sequence (mutations are found in most colon carcinomas but rarely in adenomas).

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice C) *KRAS* protooncogene mutation is responsible for the increase in size of adenomatous polyps and also leads to uncontrolled cell growth. Such mutations tend to occur prior to *TP53* mutations.

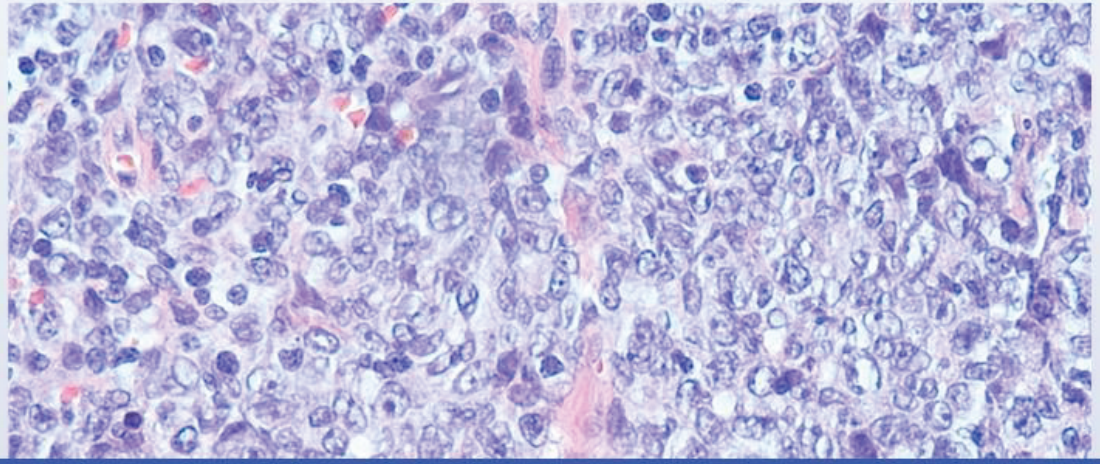
(Choice D) *NMYC* is an oncogene. An increased number of copies of this gene (amplification) are seen in neuroblastoma.

(Choice F) Mutation of *WT1*, a tumor suppressor gene, leads to the development of Wilms tumor.

Educational objective:
The adenoma to carcinoma sequence is a series of gene mutations that leads to the development of colon adenocarcinoma. *TP53* tumor suppressor gene mutation is part of the final step in the sequence and leads to malignant transformation of preexisting large adenomatous polyps.

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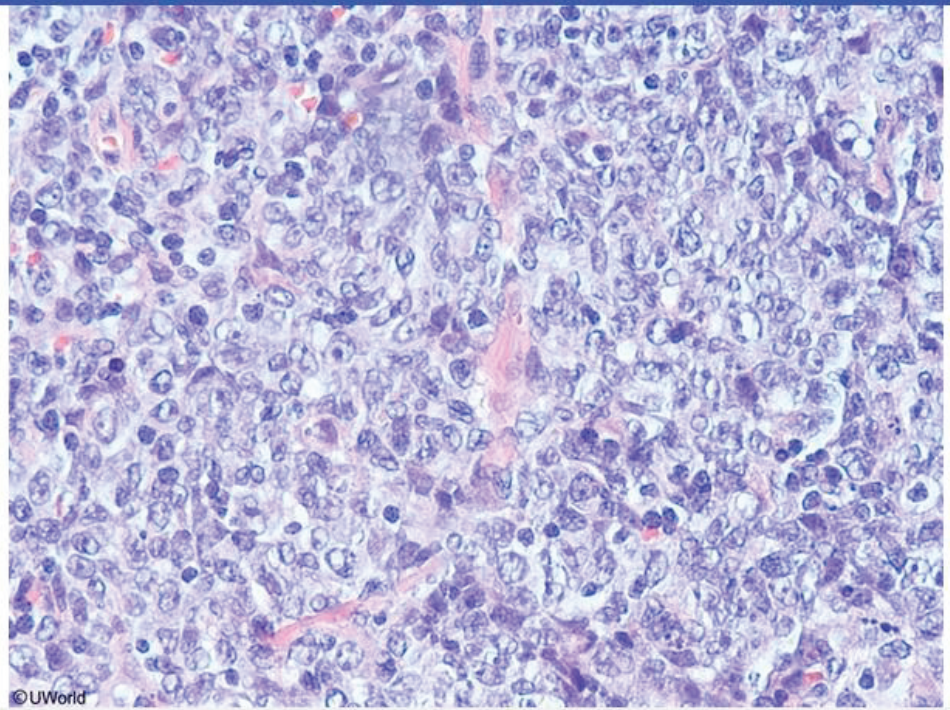
A 13-year-old boy is admitted to the hospital due to fever and fatigue for the past week. The patient recently received a cadaveric renal transplant for glomerulonephritis, and his immunosuppressive medication regimen was increased a month ago due to early evidence of rejection. Temperature is 37.7 C (99.9 F). Heart and lung examinations are unremarkable. The liver is mildly enlarged, and the spleen tip is palpable. There is notable adenopathy of the bilateral inguinal and axillary regions. A complete blood count shows mild leukopenia. Histopathology findings from biopsy of one of the enlarged lymph nodes are shown in the image below.



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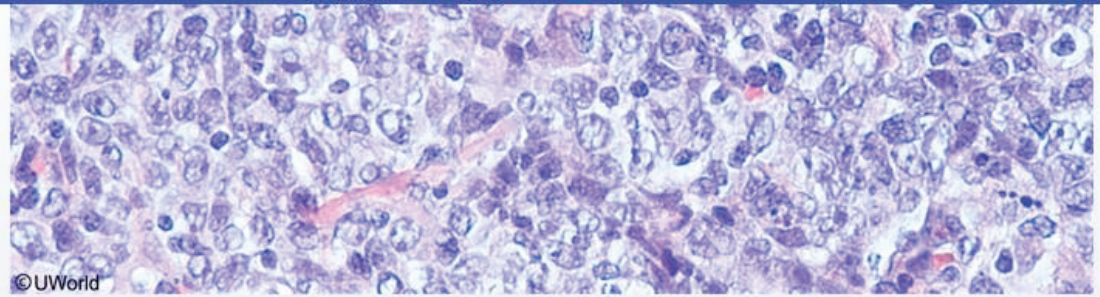
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Which of the following is the most likely cause of this patient's presentation?

A. *Aspergillus fumigatus*

B. *Bartonella henselae*

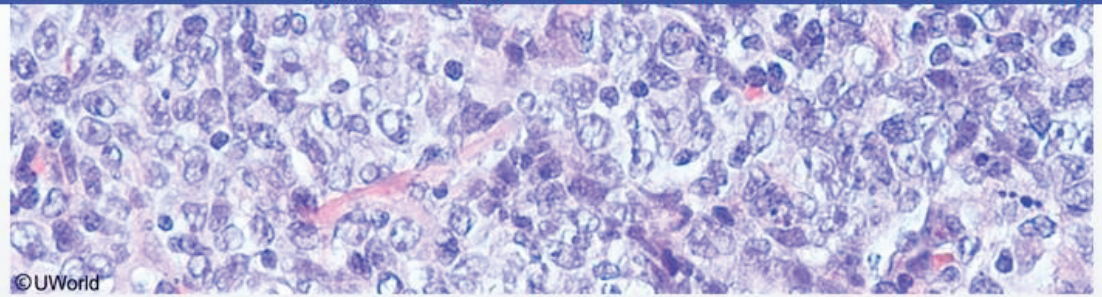
C. *Cryptococcus neoformans*

D. Epstein-Barr virus

E. Parvovirus B19

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Which of the following is the most likely cause of this patient's presentation?

- A. *Aspergillus fumigatus* (5%)
- B. *Bartonella henselae* (12%)
- C. *Cryptococcus neoformans* (2%)
- ✓ D. Epstein-Barr virus (71%)
- E. Parvovirus B19 (7%)

Correct

71%
Answered correctly

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Posttransplantation lymphoproliferative disorder	
Etiology	• Immunosuppression following solid-organ or hematopoietic stem cell transplantation → suppressed cytotoxic T-cell immunosurveillance → Epstein-Barr virus–encoded proteins drive unchecked B-cell growth/expansion
Manifestations	• Mononucleosis-like symptoms (eg, fever, night sweats, hepatosplenomegaly, lymphadenopathy) • Extranodal mass in approximately 50% • Biopsy findings: polyclonal or monoclonal B-cell proliferation

This patient underwent solid organ transplantation and is on high-dose immunosuppressive medications due to acute graft rejection. He subsequently developed **mononucleosis-like symptoms** (eg, fever, night sweats, lymphadenopathy, hepatosplenomegaly, leukopenia) with biopsy showing large, atypical B cells completely effacing the lymph node architecture. This constellation of findings likely indicates **posttransplantation lymphoproliferative disorder** (PTLD).

PLTD is a plasmocytic or lymphoid proliferation that occurs in the weeks or months following solid-organ or

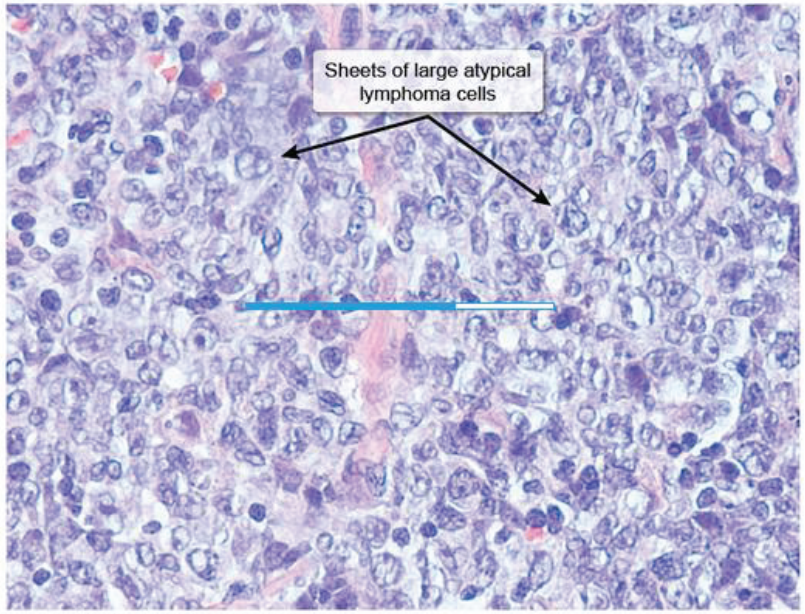
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Etiology

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Diffuse large B-cell lymphoma*



*Most common type of non-Hodgkin lymphoma.

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EBV replication promotes **B-cell proliferation** due to the expression of viral membrane proteins (latent

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PLTD is a plasmocytic or lymphoid proliferation that occurs in the weeks or months following solid-organ or hematopoietic stem cell transplantation. It is generally caused by proliferation of **Epstein-Barr virus** (EBV) in donor or host cells due to **reduced cytotoxic T-cell immunosurveillance** from high dose **immunosuppressive therapy**.

EBV replication promotes **B-cell proliferation** due to the expression of viral membrane proteins (latent membrane protein 1/2A) that mimic B-cell antigen stimulation signals; it also promotes **B-cell survival** due to the expression of viral nuclear transcription factors (EBNA-2/LP) that activate host survival genes. These virus-mediated changes generate **immortalized plasmocytic or lymphoid cells** that proliferate widely in the reticuloendothelial system, leading to lymphadenopathy, hepatosplenomegaly, and B-symptoms (eg, fever, night sweats).

(Choice A) Invasive aspergillosis is common in those with profound neutropenia following transplantation. However, it primarily affects the lung (not lymph nodes) and is marked by fungi with septate hyaline hyphae and acute angle branching. Tissue necrosis, hemorrhage, and invasion of tissue planes are prominent.

(Choice B) *Bartonella henselae* infection causes cat-scratch disease, which is associated with regional lymphadenopathy. Histopathology demonstrates necrotizing granulomatous adenitis with multinucleated giant cells, stellate granulomas, and microabscesses. Specialized stains can reveal the bacterium.

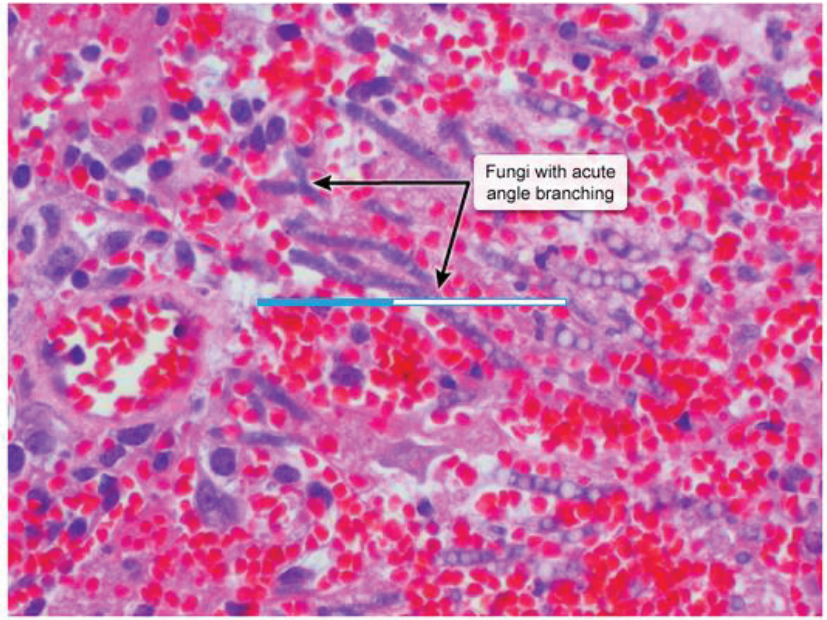
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PLTD is a plasmocytic or lymphoid proliferation that occurs in the weeks or months following solid organ or

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Invasive aspergillosis



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lymphadenopathy. Histopathology demonstrates necrotizing granulomatous adenitis with multinucleated giant cells, stellate granulomas, and microabscesses. Specialized stains can reveal the bacterium.

(Choice C) Patients with severe immunocompromisation from AIDS or immunosuppressive medications can develop *Cryptococcus neoformans* infection, which usually presents with meningoencephalitis (eg, headache, vomiting, confusion) or pneumonitis. Disseminated infection is less common and primarily affects the skin and skeletal system. In addition, histopathology will show budding, encapsulated yeasts.

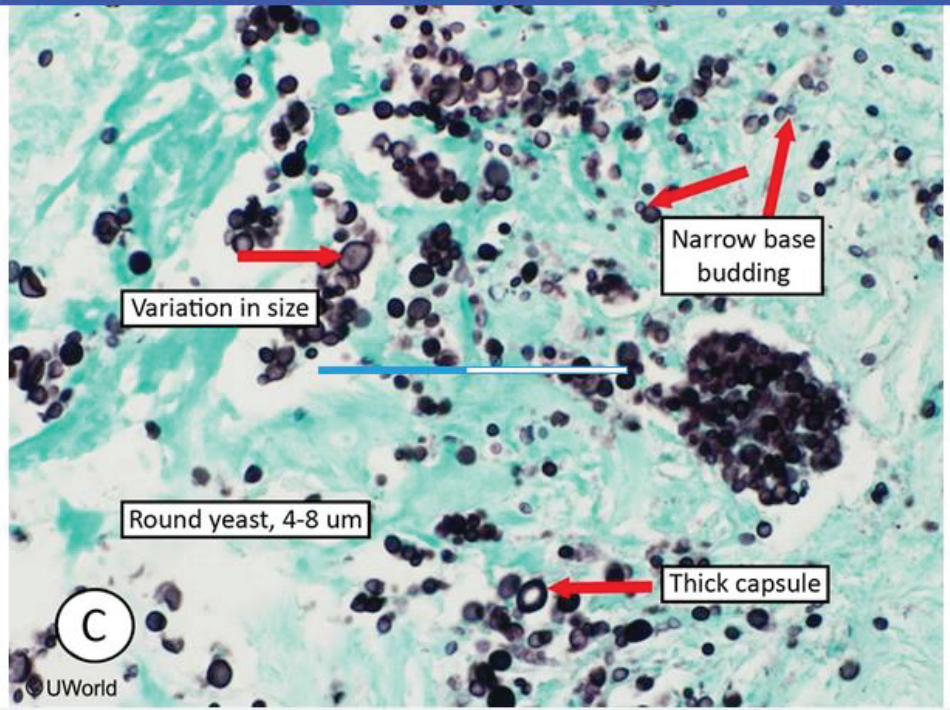
(Choice E) Chronic or reactivated parvovirus infection can occur in severely immunosuppressed individuals. Although this frequently causes fever, fatigue, and (sometimes) leukopenia, most cases are marked by severe anemia due to red cell aplasia. In addition, generalized lymphadenopathy would be atypical.

Educational objective:
Posttransplantation lymphoproliferative disorder occurs in patients who have undergone solid-organ or stem cell transplantation and are taking high-dose immunosuppressive medications. Most cases are caused by the reactivation of Epstein-Barr virus, which generates viral proteins that stimulate B-cell proliferation and survival. Patients usually have mononucleosis-like symptoms.

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A 28-year-old woman comes to the physician after finding a lump in her right breast. Her mother died from ovarian cancer at age 34 and her aunt died from breast cancer at age 32. After the appropriate workup, she is diagnosed with breast cancer. This patient most likely inherited a mutation in a gene normally responsible for which of the following processes?

A. Angiogenesis
B. DNA repair
C. Intercellular adhesion
D. Protein degradation
E. Signal transduction

Submit

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A 28-year-old woman comes to the physician after finding a lump in her right breast. Her mother died from ovarian cancer at age 34 and her aunt died from breast cancer at age 32. After the appropriate workup, she is diagnosed with breast cancer. This patient most likely inherited a mutation in a gene normally responsible for which of the following processes?

A. Angiogenesis (1%)
✓ B. DNA repair (65%)
C. Intercellular adhesion (2%)
D. Protein degradation (2%)
E. Signal transduction (27%)

Correct
65% Answered correctly
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Explanation

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Proto-oncogenes 1-hit GAIN of function		Tumor suppressor genes 2-hit LOSS of function	
RAS (GTP-binding protein)	• Cholangiocarcinoma • Pancreatic adenocarcinoma	***BRCA1/2*** (DNA repair genes)	• Breast & ovarian cancer
MYC (Transcription factor)	• Burkitt lymphoma	***APC/β-catenin*** (Wnt signaling pathway)	• Colon, gastric & pancreatic cancer • Familial adenomatous polyposis
ERBB1 (EGFR) (Receptor tyrosine kinase)	• Lung adenocarcinoma	***TP53*** (Genomic stability)	• Most cancers • Li-Fraumeni syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma

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kinase)			syndrome
ERBB2 (HER2) (Receptor tyrosine kinase)	• Breast cancer	***RB*** (G_1/S transition inhibitor)	• Retinoblastoma • Osteosarcoma
ABL (Nonreceptor tyrosine kinase)	• Chronic myelogenous leukemia	***WT1*** (Urogenital differentiation)	• Wilms tumor
BRAF (Ras signal transduction)	• Hairy cell leukemia • Melanoma	***VHL*** (Ubiquitin ligase component)	• Renal cell carcinoma • Von Hippel-Lindau syndrome

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The majority of breast cancer cases occur sporadically in women age >50. **Hereditary breast cancer** should be suspected in patients diagnosed at a young age, patients with 2 or more primary breast and/or ovarian cancers, and individuals with multiple family members affected by early-onset breast or ovarian cancer. Most cases of hereditary breast and ovarian cancer are associated with mutations in the tumor

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should be suspected in patients diagnosed at a young age, patients with 2 or more primary breast and/or ovarian cancers, and individuals with multiple family members affected by early-onset breast or ovarian cancer. Most cases of hereditary breast and ovarian cancer are associated with mutations in the tumor suppressor genes ***BRCA1*** and ***BRCA2***. Tumor suppressor genes are involved in multiple processes, including:

1. DNA repair
2. Cellular differentiation
3. Checkpoint control of the cell cycle
4. Transcription factor regulation

BRCA1 and BRCA2 in particular are involved in repair of **double-stranded DNA breaks**. Mutations in *BRCA1* and *BRCA2* result in genetic instability, predisposing cells to an increased risk of malignant transformation. Both *BRCA* mutations are inherited in an **autosomal dominant** manner with variable penetrance. Affected women have a **70%-80% lifetime risk** for developing breast cancer. Moreover, their lifetime risk of developing ovarian cancer is also increased by up to 40%, although the *BRCA2* gene is less likely to lead to ovarian cancer.

(Choice A) Angiogenesis is an essential factor in the growth of tumors due to their rapid rate of division and high metabolic demands. Although they stimulate angiogenesis by increasing production of

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likely to lead to ovarian cancer.

(Choice A) Angiogenesis is an essential factor in the growth of tumors due to their rapid rate of division and high metabolic demands. Although they stimulate angiogenesis by increasing production of substances such as vascular endothelial growth factor, tumors frequently outgrow their blood supply and become necrotic in the center.

(Choice C) Intercellular adhesion is impaired in the majority of malignant tumors, which allows portions of the tumor to break off and metastasize. Adhesion molecules such as E-cadherin are also responsible for transduction of growth signals important for normal tissue growth and regeneration; disruption of intercellular adhesion signaling can promote unchecked cellular proliferation.

(Choice D) Protein degradation is essential for regulation of cellular functions and is performed by the proteasome as well as cytosolic proteinases. Increased degradation of protective proteins such as p53 or decreased breakdown of proteins that favor cell division can lead to malignancy.

(Choice E) A large number of malignancies are associated with aberrant signal transduction. For example, overexpression of HER2 (a receptor tyrosine kinase involved in growth signal transduction) causes the development of certain types of aggressive breast cancer. Unlike *BRCA1* and *BRCA2*, *HER2* mutations are acquired, not inherited.

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intercellular adhesion signaling can promote unchecked cellular proliferation.

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Educational objective:

Hereditary breast cancer is most commonly associated with mutations in *BRCA1* and *BRCA2*. These tumor suppressor genes are involved in DNA repair, and their mutation increases the risk of developing breast and ovarian cancer.

References

- Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE.

Pathology Pathology (General Principles) Breast cancer

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A 68-year-old man comes to the office due to persistent back pain for the past several months. He is a retired veteran and has not seen a doctor for many years. He has smoked a pack of cigarettes daily for 36 years. His blood pressure is 145/85 mm Hg and pulse is 88/min and regular. Cardiopulmonary examination is unremarkable. The abdomen is soft and nontender. There is focal tenderness over the 10th rib and L1-L2 vertebral region. Neurologic examination is normal. Radionuclide bone imaging reveals increased activity in multiple vertebrae and ribs, corresponding to the patient's painful areas. Routine radiographs show sclerotic lesions matching the bone scan areas of increased uptake, which are highly suspicious for metastatic cancer. Which of the following additional findings is most likely to be seen in this patient?

A. Hematuria and polycythemia
B. Monoclonal immunoglobulin spike
C. Lung mass and elevated parathyroid hormone-related peptide
D. Lymphadenopathy and BCL-2 overexpression
E. Nodular prostate and elevated prostate-specific antigen level

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B. Monoclonal immunoglobulin spike
C. Lung mass and elevated parathyroid hormone-related peptide
D. Lymphadenopathy and BCL-2 overexpression
E. Nodular prostate and elevated prostate-specific antigen level
F. Rapidly enlarging, large, irregular mole

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examination is unremarkable. The abdomen is soft and nontender. There is focal tenderness over the 10th rib and L1-L2 vertebral region. Neurologic examination is normal. Radionuclide bone imaging reveals increased activity in multiple vertebrae and ribs, corresponding to the patient's painful areas. Routine radiographs show sclerotic lesions matching the bone scan areas of increased uptake, which are highly suspicious for metastatic cancer. Which of the following additional findings is most likely to be seen in this patient?

A. ~~Hematuria and polycythemia~~ (2%)

B. ~~Monoclonal immunoglobulin spike~~ (18%)

C. ~~Lung mass and elevated parathyroid hormone-related peptide~~ (12%)

D. ~~Lymphadenopathy and BCL-2 overexpression~~ (1%)

✓ E. Nodular prostate and elevated prostate-specific antigen level (64%)

F. Rapidly enlarging, large, irregular mole (0%)

Correct

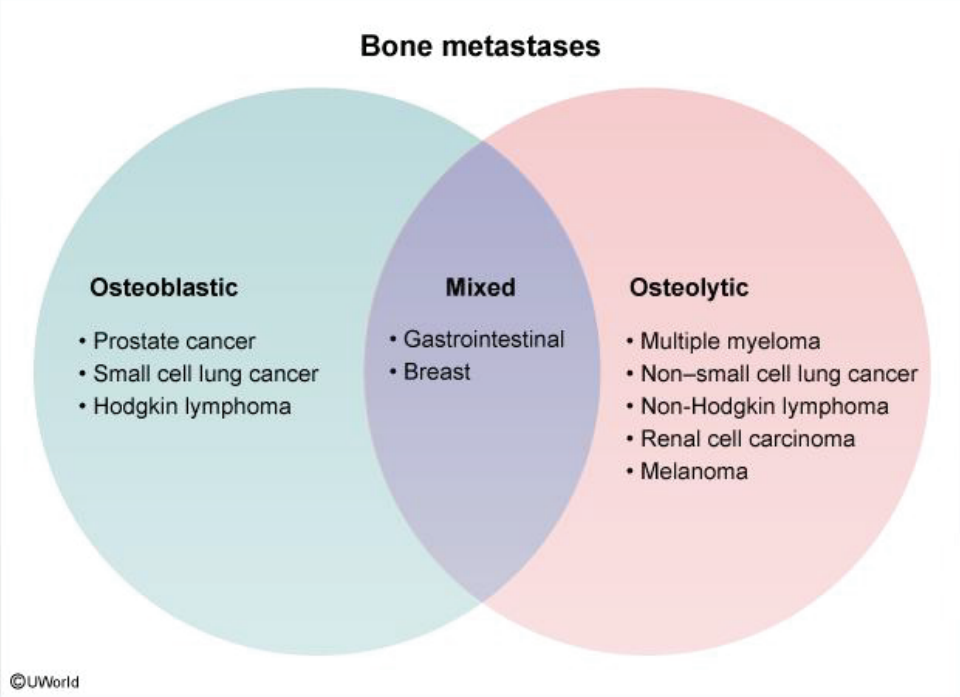
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This patient with sclerotic bony metastases most likely has prostate cancer. Imaging of **bone metastases** assists in cancer diagnosis, as it allows the lesions to be characterized as:

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This patient with sclerotic bony metastases most likely has prostate cancer. Imaging of **bone metastases** assists in cancer diagnosis, as it allows the lesions to be characterized as:

- **Osteolytic (lucent):** Due to osteoclast stimulation, tend to represent aggressive cancer
- **Osteoblastic (sclerotic):** Due to osteoblasts, indicates a more indolent course

Metastatic **prostate cancer** commonly has **osteoblastic** (sclerotic) bone lesions. Bone pain is a typical clinical presentation; other symptoms include cancer cachexia and urinary symptoms (which are not always present). Prostate cancer is the most common non-skin cancer in men, and African American men are at highest risk. An irregular prostate gland on digital rectal examination is suggestive of the diagnosis, which is then confirmed by biopsy. The prostate-specific antigen tumor marker is commonly elevated.

(Choice A) Hematuria and polycythemia (due to erythropoietin release) are suggestive of renal cell cancer. Renal cell cancer bone metastases are commonly osteolytic.

(Choice B) Monoclonal immunoglobulin spikes are found in multiple myeloma. Myeloma cells suppress osteoblasts and would cause osteolytic lesions, which are not present in this patient. Patients commonly have bone pain, recurrent infections, and symptoms of anemia.

(Choice C) Elevated parathyroid hormone-related peptide (PTH-rP) levels can occur with non-small cell

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have bone pain, recurrent infections, and symptoms of anemia.

(Choice C) Elevated parathyroid hormone-related peptide (PTH-rP) levels can occur with non-small cell lung cancer (NSCLC) and are associated with symptoms of hypercalcemia (confusion, abdominal pain, bony pain). Osteolytic bone lesions would be seen in NSCLC.

(Choice D) Lymphadenopathy and BCL-2 overexpression are found in lymphomas. BCL-2 is an anti-apoptosis factor, and overexpression plays a role in resistance to chemotherapy. Common manifestations of lymphoma also include night sweats, weight loss, and fatigue.

(Choice F) A rapidly enlarging irregular mole is suggestive of a melanoma. The liver, bone, and brain are the most common metastatic sites. Melanoma causes lytic bone lesions.

Educational objective:
Imaging of bone metastases assists in cancer diagnosis. Bone metastases are characterized as osteolytic or osteoblastic. Bony pain in an older man with osteoblastic lesions on imaging is highly suspicious for prostate cancer.

References

- Mechanism of bone metastasis.

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A 48-year-old woman comes to the office due to a sore throat for the past 3 months. On examination, she is found to have an enlarged, ulcerated left tonsil and a firm, nontender, nonmobile left neck mass. The patient undergoes biopsy of the tonsil. Pathology is consistent with squamous cell carcinoma. Further analysis of the biopsy specimen shows expression of viral genome proteins. Which of the following most likely predisposed the patient to the development of this malignancy?

A. Decreased activity of *BRAF*-associated protein

B. Decreased activity of *RB*-associated protein

C. Decreased activity of *RET*-associated protein

D. Overexpression of *BRCA1*- or *BRCA2*-associated protein

E. Overexpression of *MEN1*-associated protein

Submit

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A 48-year-old woman comes to the office due to a sore throat for the past 3 months. On examination, she is found to have an enlarged, ulcerated left tonsil and a firm, nontender, nonmobile left neck mass. The patient undergoes biopsy of the tonsil. Pathology is consistent with squamous cell carcinoma. Further analysis of the biopsy specimen shows expression of viral genome proteins. Which of the following most likely predisposed the patient to the development of this malignancy?

- ✗ A. Decreased activity of *BRAF*-associated protein (19%)
- ✓ B. Decreased activity of *RB*-associated protein (61%)
- C. ~~Decreased activity of *RET*-associated protein~~ (12%)
- D. ~~Overexpression of *BRCA1*- or *BRCA2*-associated protein~~ (1%)
- E. ~~Overexpression of *MEN1*-associated protein~~ (4%)

Incorrect
Correct answer
B

61%
Answered correctly

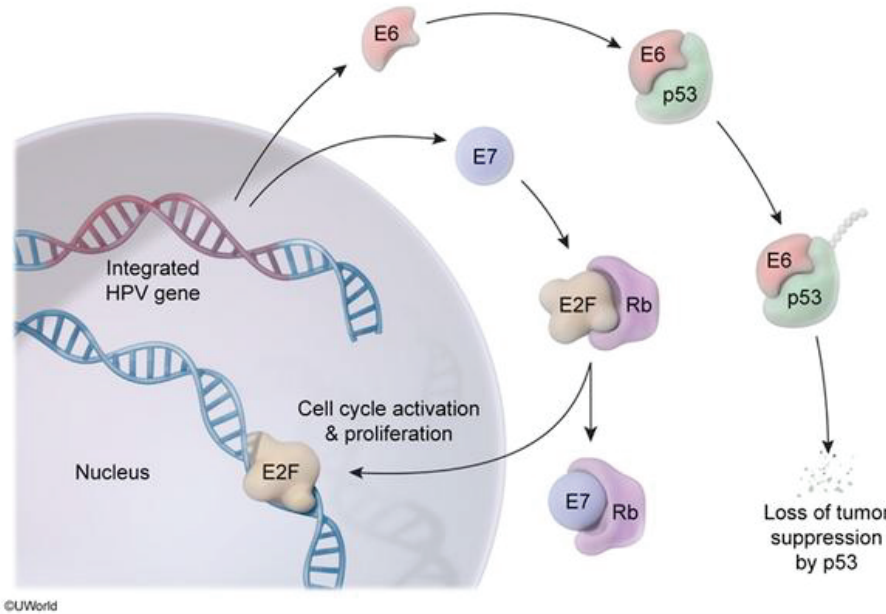
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Molecular basis of HPV oncogenesis

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Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two

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Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two types of genes can be altered to increase malignant potential:

- **Protooncogenes** (eg, *RET*), which require **gain-of-function** mutations to convert to oncogenes. They typically encode proteins that **promote cell division** (eg, growth factors, receptors, signal transduction factors). Only one allele must be damaged to increase the risk of cancer formation.
- **Tumor suppressor** genes (eg, *TP53*, *RB*), in which **loss of function** results in unregulated growth. They typically encode proteins involved in apoptosis or inhibition of cell cycle progression; both alleles must be inactivated to increase the risk of malignancy.

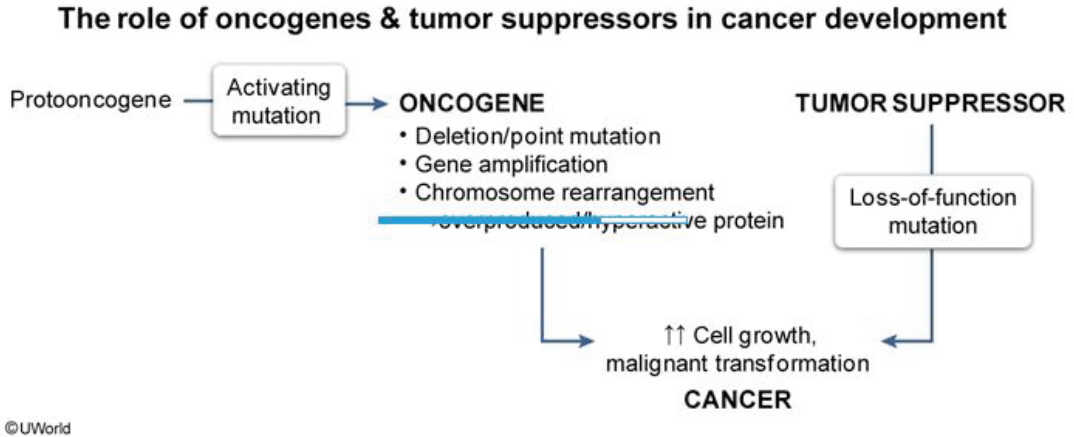
Oncoviruses can induce cancer-forming mutations through the expression of proteins that activate protooncogenes or inactivate tumor suppressor genes. Human papillomavirus (HPV) is implicated in several types of cancer, including head and neck, cervical, anal, and penile cancer. HPV produces **viral oncoproteins E6 and E7**, both of which affect tumor suppressors:

- HPV viral protein E6 binds to p53, a tumor suppressor protein that normally inhibits the proliferation of cells with genetic abnormalities. Ubiquitination of the E6-p53 complex induces **degradation of p53**, leading to unregulated cellular growth.
- HPV viral protein E7 **binds to** retinoblastoma **(Rb)** protein, which results in the displacement of E2F (a transcription factor that induces cell cycle activation), promoting unregulated DNA replication and

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Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two

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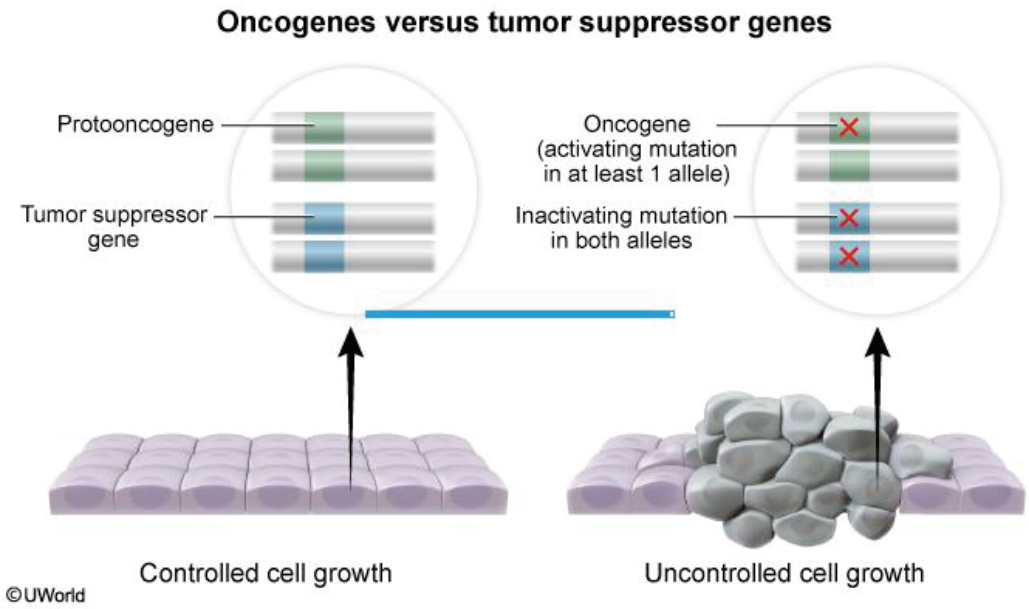
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transcription factor that induces cell cycle activation), promoting unregulated DNA replication and

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Tumor formation is driven by the accumulation of mutations that lead to **uncontrolled cell growth**. Two

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transcription factor that induces cell cycle activation), promoting unregulated DNA replication and

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leading to unregulated cellular growth.

- HPV viral protein E7 **binds to** retinoblastoma **(Rb)** protein, which results in the displacement of E2F (a transcription factor that induces cell cycle activation), promoting unregulated DNA replication and cyclin-mediated cell cycling.

(Choices A and C) *BRAF* encodes for a serine/threonine–specific protein kinase involved in regulating the mitogen-activated protein kinase signaling pathway. It is often mutated in melanoma, non-Hodgkin lymphoma, and papillary thyroid cancer. *RET* encodes for a receptor tyrosine kinase and is associated with multiple endocrine neoplasia (MEN) 2A, MEN 2B, and papillary thyroid cancer. Both *RET* and *BRAF* are protooncogenes that require gain-of-function mutations to become oncogenes. Decreased activity can protect against uncontrolled proliferation (eg, BRAF inhibitors used in melanoma).

(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA repair protein. *MEN1* (associated with MEN1) encodes for the protein menin, which has diverse functions that may be related to regulation of cell cycle kinase inhibitor and homeobox genes. Both *BRCA1/2* and *MEN1* are tumor suppressor genes, meaning that their inactivation (rather than overexpression) leads to tumor development.

Educational objective:

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(Choices D and E) *BRCA1* and *BRCA2* (associated with breast, ovarian, and pancreatic cancers) encode a DNA repair protein. *MEN1* (associated with MEN1) encodes for the protein menin, which has diverse functions that may be related to regulation of cell cycle kinase inhibitor and homeobox genes. Both *BRCA1/2* and *MEN1* are tumor suppressor genes, meaning that their inactivation (rather than overexpression) leads to tumor development.

Educational objective:
Inactivation of retinoblastoma protein activity by human papillomavirus can lead to the formation of head and neck squamous cell carcinoma.

References

- The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis.
- The molecular landscape of head and neck cancer.

Pathology	Pathology (General Principles)	Oncogenes and tumor suppressor genes
Subject	System	Topic

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A 47-year-old woman, gravida 2 para 2, comes to the office after noticing a pea-sized lump in her right breast while taking a shower. Her medical history is significant for 3 pack-years of cigarette use during her 20s. She underwent infertility treatment and in vitro fertilization for both of her pregnancies. The patient has no family history of breast or ovarian cancer. A clinical breast examination confirms the presence of a firm, fixed nodule in the right breast with a small patch of overlying puckered skin. Mammogram findings are highly suspicious for malignancy, and a needle biopsy reveals infiltrating ductal carcinoma. A right mastectomy and axillary lymph node dissection are scheduled. Overexpression of which of the following markers is most likely to be associated with aggressive disease in this patient?

A. BCL-2
B. Estrogen receptor
C. HER2
D. Mutated p53
E. Progesterone receptor

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breast while taking a shower. Her medical history is significant for 3 pack-years of cigarette use during her 20s. She underwent infertility treatment and in vitro fertilization for both of her pregnancies. The patient has no family history of breast or ovarian cancer. A clinical breast examination confirms the presence of a firm, fixed nodule in the right breast with a small patch of overlying puckered skin. Mammogram findings are highly suspicious for malignancy, and a needle biopsy reveals infiltrating ductal carcinoma. A right mastectomy and axillary lymph node dissection are scheduled. Overexpression of which of the following markers is most likely to be associated with aggressive disease in this patient?

A. BCL-2 (6%)
B. Estrogen receptor (13%)
✓ C. HER2 (67%)
D. Mutated p53 (11%)
E. Progesterone receptor (1%)

Correct
67%
52 secs
10/05/2020

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Human epidermal growth factor receptor 2 (**HER2**, also called ERBB2) is a member of the epidermal growth factor receptor family. It is overexpressed in 20%-30% of **breast cancers**. HER2 is a transmembrane glycoprotein with **tyrosine kinase** activity that acts to increase cell proliferation. It is present in diminutive amounts in normal breast and ovarian cells. In breast cancer, HER2 overexpression (positivity) is associated with **poorly differentiated, rapidly growing tumors**. Clinically, HER2 status is used to predict therapeutic response to anti-HER2 monoclonal antibodies (eg, trastuzumab).

(Choice A) Overexpression of the anti-apoptotic BCL-2 protein is classically observed in follicular lymphomas, but it also occurs in a variety of other malignancies, including breast cancer. Unlike in lymphomas, increased expression of BCL-2 in breast cancer is associated with a favorable prognosis.

(Choices B and E) Breast cancers that express high levels of estrogen and/or progesterone receptors are typically associated with improved outcomes. Activation of these receptors acts as a stimulus for tumor growth. Therefore, anti-estrogen therapy (eg, aromatase inhibitors, tamoxifen) is used to treat hormone receptor-positive breast cancer.

(Choice D) Overexpression of a mutated form of p53 is found in many human cancers, including breast cancers. However, the degree of protein expression does not correlate well with clinical outcomes. Rather, the effects on prognosis are more dependent on the specific mutation (eg, nonsense, gain of function).

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(Choices B and E) Breast cancers that express high levels of estrogen and/or progesterone receptors are typically associated with improved outcomes. Activation of these receptors acts as a stimulus for tumor growth. Therefore, anti-estrogen therapy (eg, aromatase inhibitors, tamoxifen) is used to treat hormone receptor-positive breast cancer.

(Choice D) Overexpression of a mutated form of p53 is found in many human cancers, including breast cancers. However, the degree of protein expression does not correlate well with clinical outcomes. Rather, the effects on prognosis are more dependent on the specific mutation (eg, nonsense, gain of function).

Educational objective:

Estrogen- or progesterone-receptor positivity in breast cancer indicates expected sensitivity to tamoxifen and aromatase inhibitor treatment. HER2 overexpression in breast cancer suggests a more aggressive tumor that typically responds to therapy with the anti-HER2 monoclonal antibody trastuzumab.

References

- American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer.

Pathology	Pathology (General Principles)	Breast cancer
Subject	System	Topic

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A 61-year-old man comes to the office due to 4 months of easy fatigability, anorexia, and a 4.5-kg (10-lb) unintentional weight loss. His stool occult blood testing is positive, and laboratory studies show microcytic hypochromic anemia. Colonoscopy reveals a 6-cm (2.4-in) mass in the descending colon. Biopsy samples obtained during the procedure are consistent with adenocarcinoma. A subsequent CT scan of the abdomen shows multiple metastatic liver lesions. Therapy with monoclonal antibodies that bind to epidermal growth factor receptors on the malignant cells is considered. An activating mutation in which of the following will most likely make this therapy ineffective?

A. Adenomatous polyposis coli protein
B. KRAS protein
C. p53 protein
D. Platelet-derived growth factor
E. Vascular endothelial growth factor

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A 61-year-old man comes to the office due to 4 months of easy fatigability, anorexia, and a 4.5-kg (10-lb) unintentional weight loss. His stool occult blood testing is positive, and laboratory studies show microcytic hypochromic anemia. Colonoscopy reveals a 6-cm (2.4-in) mass in the descending colon. Biopsy samples obtained during the procedure are consistent with adenocarcinoma. A subsequent CT scan of the abdomen shows multiple metastatic liver lesions. Therapy with monoclonal antibodies that bind to epidermal growth factor receptors on the malignant cells is considered. An activating mutation in which of the following will most likely make this therapy ineffective?

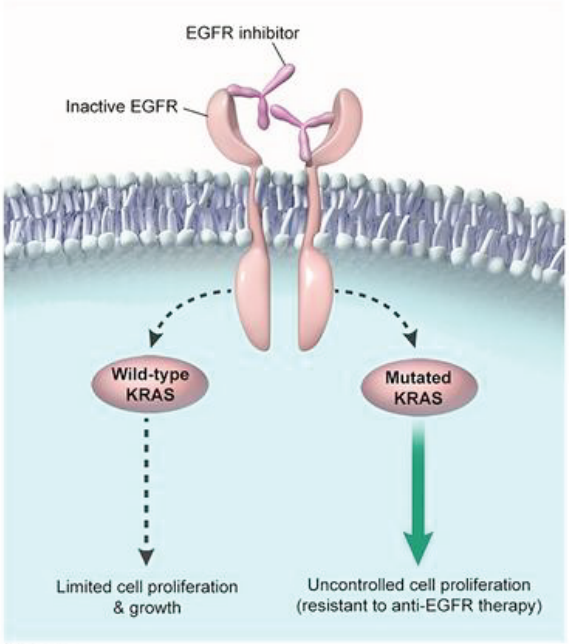
A. Adenomatous polyposis coli protein (6%)
B. KRAS protein (56%)
C. p53 protein (11%)
D. Platelet-derived growth factor (7%)
E. Vascular endothelial growth factor (17%)

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KRAS mutation causing anti-EGFR resistance



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Epidermal growth factor receptor (EGFR) is stimulated in a paracrine or autocrine fashion by its ligands, leading to the **downstream activation of KRAS**, a membrane-bound GTP-binding protein that **stimulates cellular growth** and proliferation. Many cancers (eg, colorectal, pancreas) leverage this system to drive unchecked cellular growth by overexpressing EGFR and its ligands or by developing constitutive activating mutations in the *KRAS* proto-oncogene.

The EGFR signaling system can be targeted for cancer treatment through the use of **monoclonal antibodies** (eg, cetuximab, panitumumab) that **block EGFR**, leading to reduced KRAS stimulation and **decreased cellular growth**. However, this treatment is only effective for tumors with wild-type (normal) KRAS. Tumors with ***KRAS*-activating mutations** are **resistant** to anti-EGFR agents as they have a constitutive activation of a downstream signal that is independent of EGFR stimulation or blockade. Prior to the use of anti-EGFR agents, genetic testing of tumor tissue is performed to see if KRAS is wild-type (eligible for treatment) or mutated (noneligible).

(Choice A) Adenomatous polyposis coli is a tumor suppressor protein that helps degrade beta-catenin, preventing uncontrolled cell growth. Inherited inactivating gene mutations are responsible for familial adenomatous polyposis.

(Choice C) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control; mutations or deletions are present in a large percentage of human tumors

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adenomatous polyposis.

(Choice C) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control; mutations or deletions are present in a large percentage of human tumors.

(Choice D) Platelet-derived growth factor stimulates formation of new blood vessels and proliferation of fibroblasts and smooth muscle cells by binding to a receptor tyrosine kinase; mutations resulting in overexpression encourage tumor growth by promoting uncontrolled angiogenesis.

(Choice E) Vascular endothelial growth factor (VEGF) is the dominant growth factor involved in angiogenesis and lymph vessel development. Overexpression of VEGF promotes tumor vascularization, facilitating the growth and metastasis of cancers.

Educational objective:
Activating mutations of the *KRAS* gene lead to constitutive activation of the epidermal growth factor receptor (EGFR) pathway, promoting increased cell proliferation and growth. Tumors harboring these mutations are resistant to treatment with anti-EGFR drugs (eg, cetuximab, panitumumab).

References

- KRAS mutation testing in metastatic colorectal cancer.

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A 38-year-old man is evaluated for bloody stools, weight loss, and anemia. The patient's past medical history is unremarkable, and he does not take any medications. He uses tobacco and drinks alcohol "socially." The patient's father died of colon cancer at age 40. His younger sister suffers from endometrial cancer. Examination is remarkable for minimal right-sided abdominal tenderness without guarding to deep palpation. Stool is positive for occult blood. Colonoscopy shows a right-sided ulcerative colon mass. No polyps are noted. Biopsy of the mass reveals adenocarcinoma. A mutation in which of the following genes is most likely responsible for this patient's condition?

- A. *APC*
- B. *BRCA1*
- C. *MEN1*
- D. *MSH2*
- E. *VHL*

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- A. ~~*APC*~~ (41%)
- B. ~~*BRCA1*~~ (5%)
- C. ~~*MEN1*~~ (1%)
- ✓ D. *MSH2* (47%)
- E. *VHL* (4%)

47% 01 min, 06 secs 01/23/2021

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Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
		• Sarcomas	

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Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	(**second hit**) leads to loss of heterozygosity & **malignant transformation**
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

This case is typical of **hereditary nonpolyposis colon cancer** (HNPCC), or Lynch syndrome, an

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		(MEN2A)	growth

This case is typical of **hereditary nonpolyposis colon cancer** (HNPCC), or Lynch syndrome, an **autosomal dominant** genetic predisposition to colon cancer. In patients with HNPCC, **colon cancer** occurs at a young age (**age <50**). **Family history** reveals a high incidence of **colon** cancer and, occasionally, **extraintestinal** (eg, endometrial) cancers in first-degree relatives.

With HNPCC, there is an inherited mutation in one of the genes responsible for **DNA mismatch repair** (eg, *MSH2, MLH1*). The products of these genes proofread DNA during replication. Patients with HNPCC inherit a mutation in an allele, and mutation of the second allele occurs during adult life. When 2 dysfunctional copies are present, malignancies will develop readily.

(Choice A) The *APC* gene is responsible for intercellular attachment. Its mutation leads to the formation of adenomatous polyps from normal mucosa. *APC* mutation is detected in most sporadic colon cancers and in all familial polyposis syndromes but not in HNPCC.

(Choice B) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice C) *MEN1* mutations are associated with multiple endocrine neoplasia type 1 syndrome (parathyroid, pituitary, and pancreatic adenomas)

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(Choice A) The *APC* gene is responsible for intercellular attachment. Its mutation leads to the formation of adenomatous polyps from normal mucosa. *APC* mutation is detected in most sporadic colon cancers and in all familial polyposis syndromes but not in HNPCC.

(Choice B) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice C) *MEN1* mutations are associated with multiple endocrine neoplasia type 1 syndrome (parathyroid, pituitary, and pancreatic adenomas).

(Choice E) Mutations in the tumor suppressor gene *VHL* are classically associated with von Hippel-Lindau syndrome (hemangioblastoma, clear cell renal carcinoma, pheochromocytoma).

Educational objective:
Hereditary nonpolyposis colon cancer (HNPCC), or Lynch syndrome, leads to occurrence of colonic adenocarcinomas at a young age (age <50) along with a predisposition for extraintestinal malignancies. Mutations of DNA mismatch repair genes are responsible for HNPCC.

Pathology	Pathology (General Principles)	Lynch syndrome
Subject	System	Topic

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A 32-year-old woman comes to the office for evaluation of a breast lump. She noticed the lump a few months ago but thinks it might be getting larger. The patient has a history of right lower limb amputation at age 17 due to osteosarcoma. The patient's mother died of an adrenal tumor, and her younger sister died of leukemia. Examination of the left breast shows a 5-cm, firm immobile mass with irregular borders. Which of the following gene mutations is the most likely etiology for this patient's condition?

- A. *APC*
- B. *BRCA1*
- C. *NF2*
- D. *TP53*
- E. *RB1*

Submit

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A. *APC* (2%)
B. *BRCA1* (20%)
C. *NF2* (1%)
✓ D. *TP53* (58%)
E. *RB1* (16%)

Correct

58%
Answered correctly

34 secs
Time Spent

01/05/2021
Last Updated

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Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
		• Sarcomas	

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Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	(**second hit**) leads to loss of heterozygosity & **malignant transformation**
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**.

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		(MEN2A)	growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common. The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with this disorder are genetically predisposed to cancer development at a **young** age. Patients with Li-Fraumeni syndrome inherit one mutated allele of *TP53*, but somatic mutation of the second allele is needed for tumor development (2-hit hypothesis).

p53 plays an essential role in maintaining the integrity of the human genome by causing cells with mutant DNA to arrest in the G1/S stage of the cell cycle until the damage is repaired. Normally, cells with irreversible DNA damage are not allowed to divide and proceed to apoptosis. Without a functioning p53 protein, the defective cells divide unchecked and become cancerous.

(Choice A) The adenomatous polyposis coli (*APC*) gene mutation is found in patients with familial polyposis syndromes, sporadic colon cancer, and melanomas. *APC* is responsible for maintaining low levels of β-catenin (oncogenic protein) and for intercellular adhesion.

(Choice B) Mutation of the *BRCA1* tumor suppressor gene increases the risk for breast and ovarian cancers, and it is the most common hereditary breast cancer. This mutation is not associated with

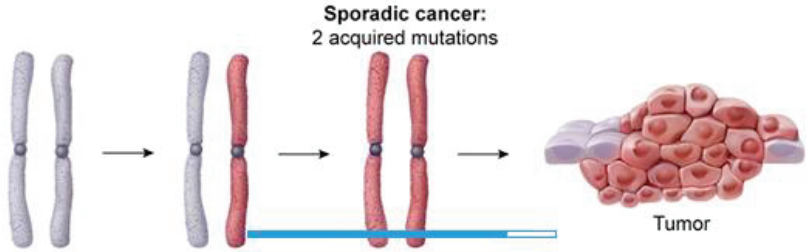
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Exhibit Display

Knudson's 2-hit hypothesis

Both copies of the gene must be knocked out to promote malignancy.

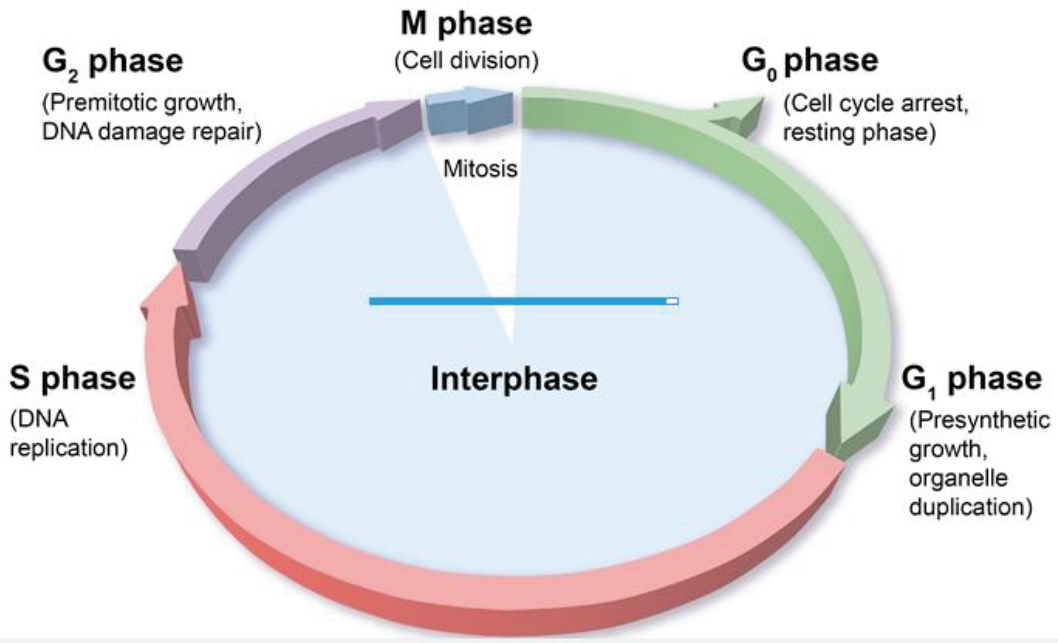


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cancers, and it is the most common hereditary breast cancer. This mutation is not associated with

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cancers, and it is the most common hereditary breast cancer. This mutation is not associated with

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levels of β-catenin (oncogenic protein) and for intercellular adhesion.

(Choice B) Mutation of the *BRCA1* tumor suppressor gene increases the risk for breast and ovarian cancers, and it is the most common hereditary breast cancer. This mutation is not associated with sarcomas, leukemia, or brain tumors.

(Choice C) *NF2* is a tumor suppressor gene. Mutation of *NF2* increases the risk for developing neurofibromatosis type 2. Patients present with bilateral acoustic neuromas (schwannomas of the cerebellopontine angle). Symptoms include bilateral hearing loss, vertigo, and tinnitus.

(Choice E) *RB1* is a tumor suppressor gene that codes for the Rb protein, which regulates the G1-S checkpoint of the cell cycle. Mutation of *RB1* predisposes to the development of retinoblastomas and osteosarcomas, but not breast cancer or leukemia. The 2-hit hypothesis has been proposed to account for hereditary retinoblastoma.

Educational objective:
Li-Fraumeni syndrome is caused by an autosomal dominant mutation in the tumor suppressor gene *TP53*. Leukemia, sarcomas, and tumors of the breast, brain, and adrenal cortex are most common.

References

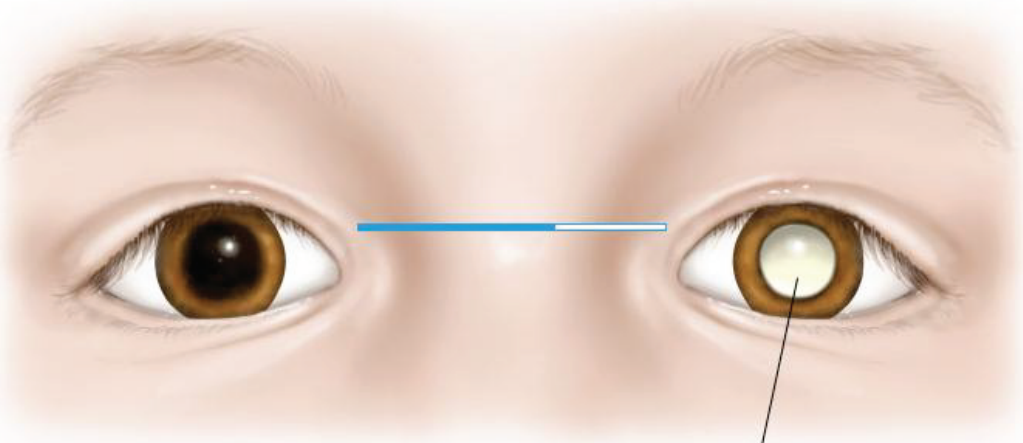
- Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers.

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levels of β-catenin (oncogenic protein) and for intercellular adhesion.

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Retinoblastoma white reflex



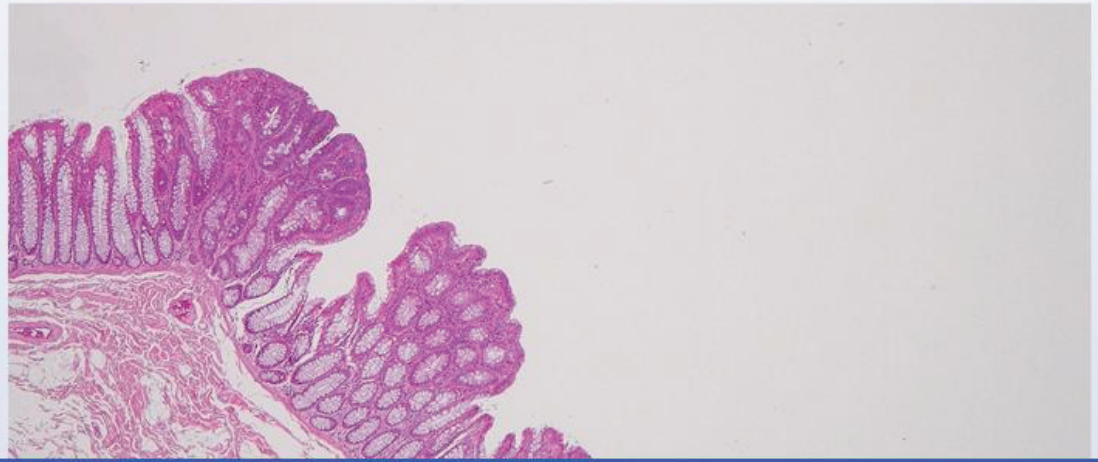
Retinoblastoma of the left eye with white reflex

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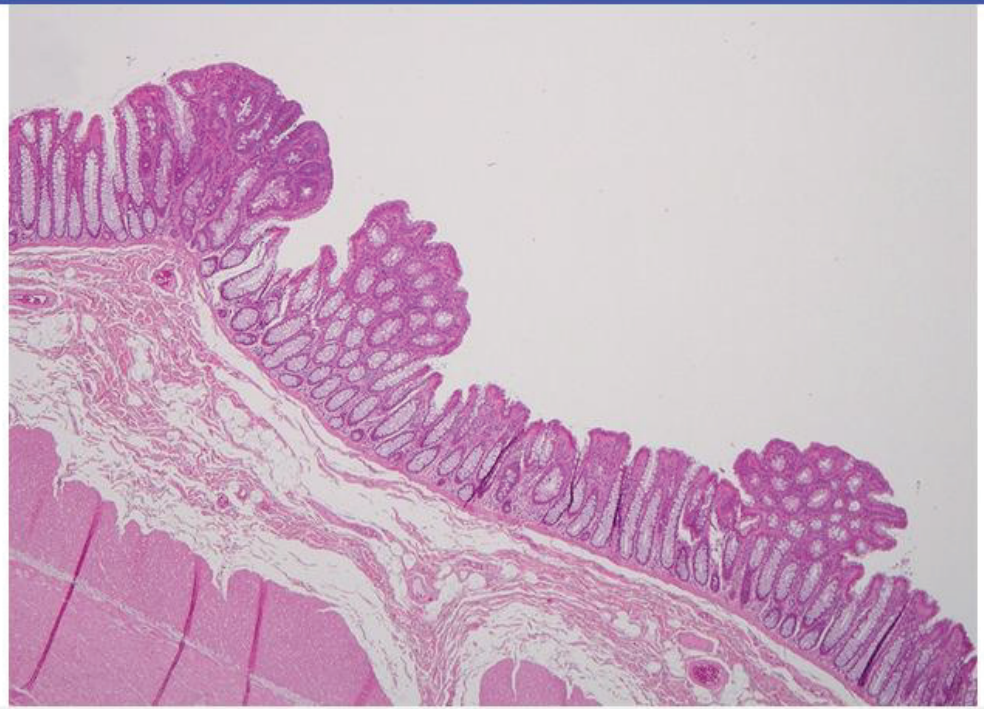
A 21-year-old woman is hospitalized for elective subtotal colectomy with ileo-rectal anastomosis due to abnormal colonoscopic findings. She underwent screening colonoscopy because of family history of colon cancer. Her maternal grandfather died of metastatic colon cancer, and her mother was also recently diagnosed with colon cancer. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. The surgery is performed with no operative complications. Numerous lesions are present throughout the resected colon, some of which are shown in the histopathology exhibit below.



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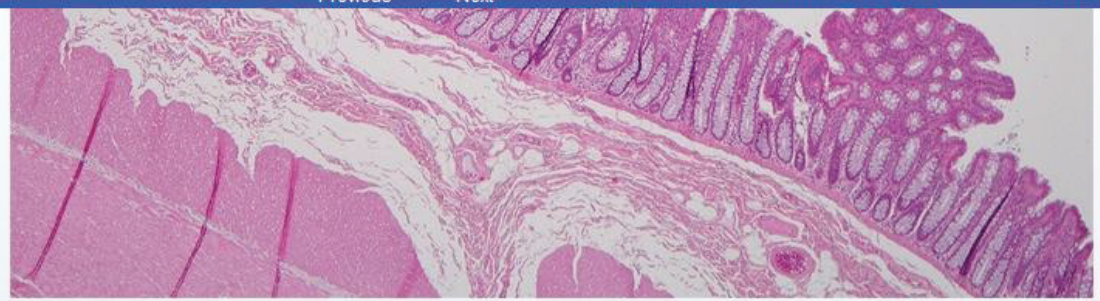
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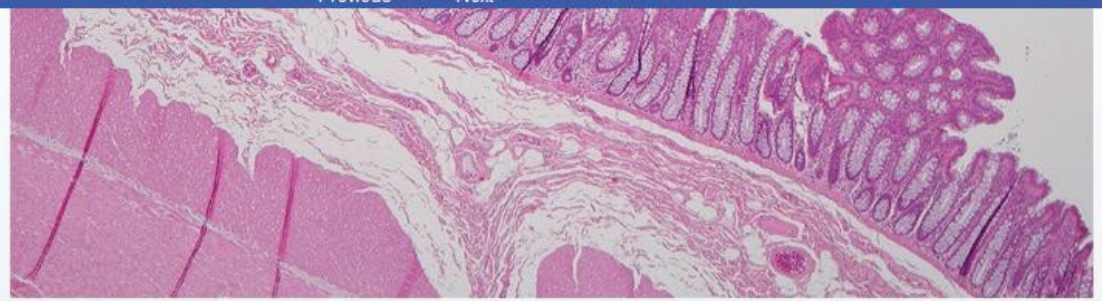


Genetic testing is most likely to reveal a germline mutation resulting in which of the following effects?

A. Abnormality of RAS signaling protein
B. Absence of regulatory *TP53* protein
C. Defective repair of DNA mismatches
D. Increase in cellular telomerase activity
E. Loss of functional APC protein

Submit

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Genetic testing is most likely to reveal a germline mutation resulting in which of the following effects?

A. Abnormality of RAS signaling protein (5%)

B. Absence of regulatory *TP53* protein (5%)

C. Defective repair of DNA mismatches (13%)

D. Increase in cellular telomerase activity (0%)

E. Loss of functional APC protein (73%)

Incorrect
Correct answer

73%

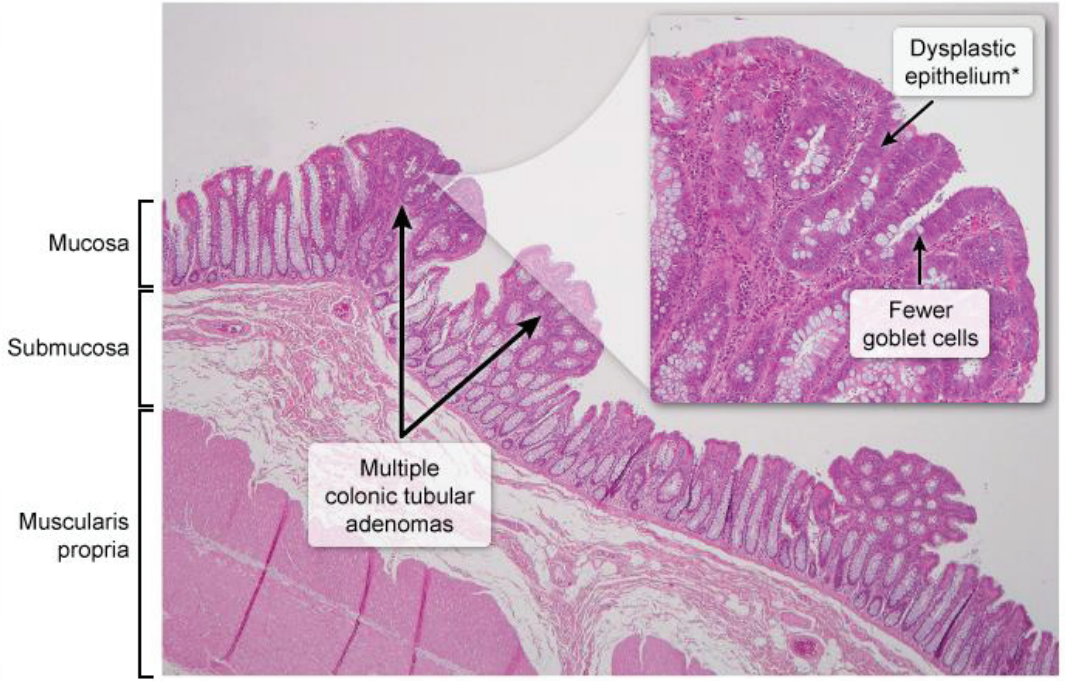
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11/11/2020

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Familial adenomatous polyposis



* Elongated, dark, crowded nuclei

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This young patient has evidence of multiple adenomas on histopathologic examination of the colon, raising strong suspicion for the autosomal dominant disorder **familial adenomatous polyposis** (FAP). Patients with FAP usually develop **innumerable colonic polyps** in the second or third decade of life. The lifetime risk that ≥1 of these polyps will transform to **invasive colon cancer** is nearly 100%. Therefore, prophylactic colectomy is usually advised.

FAP is caused by a **germline mutation** in the tumor suppressor gene *adenomatous polyposis coli* (APC). Although it is an autosomal dominant disorder, a spontaneous mutation to the other (wild-type) *APC* gene is required for expression (which usually occurs in the patient's teens or twenties). *APC* encodes for a protein that degrades beta-catenin. **Loss of function of the APC protein** increases cellular concentrations of beta-catenin, which activates transcriptional proteins that lead to intestinal crypt hyperproliferation; accumulation of subsequent mutations leads to development of polyps.

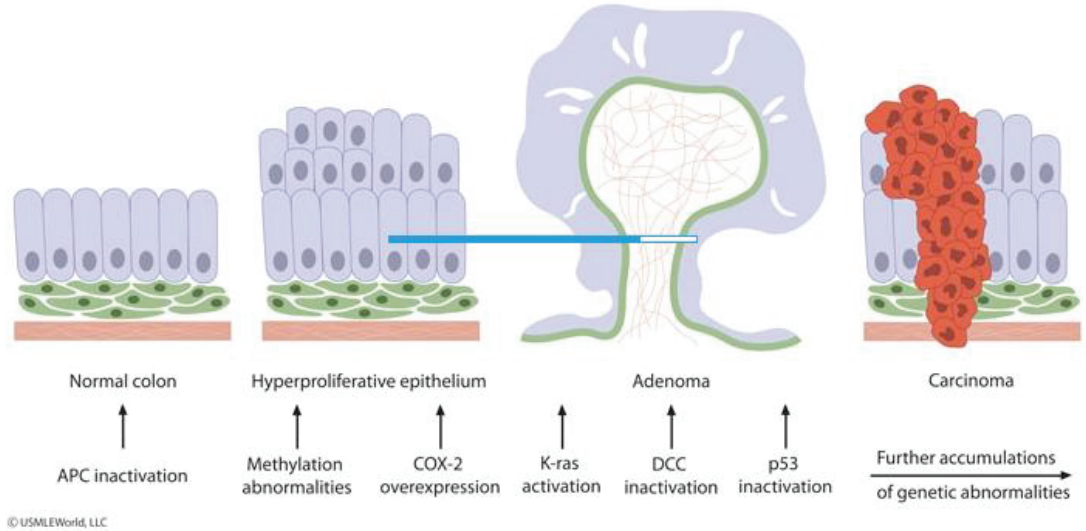
APC plays a crucial role in generation of both hereditary and spontaneous forms of colon cancer. Nearly 80% of spontaneous colon cancer has spontaneous mutations to both sets of *APC* genes; the remainder typically has activating mutations to downstream products of the *APC* pathway.

(Choice A) *RAS* oncogene mutations lead to constitutively active growth signal transduction. *RAS* mutations (particularly *KRAS*) are present in approximately 50% of sporadic colon cancers. However, FAP

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mutations (particularly *KRAS*) are present in approximately 50% of sporadic colon cancers. However, FAP

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typically has activating mutations to downstream products of the *APC* pathway.

(Choice A) *RAS* oncogene mutations lead to constitutively active growth signal transduction. *RAS* mutations (particularly *KRAS*) are present in approximately 50% of sporadic colon cancers. However, FAP is not caused by an initial mutation in *RAS*.

(Choice B) *TP53* acts as a transcriptional activator of genes that inhibit cellular growth. *TP53* mutations are the most common genetic abnormality seen in all cancers, and they are present in approximately 75% of colorectal cancers. Germline mutation to *TP53* is associated with Li Fraumeni syndrome; these patients have increased risk of many tumor types but, for unclear reasons, are not at particularly increased risk for colorectal cancer.

(Choice C) Lynch syndrome is associated with hereditary nonpolyposis colorectal cancer due to germline mutation to one of the DNA mismatch repair genes (eg, *MSH2/6*, *MLH1*). These patients do not have extensive polyposis in the colon but are very likely to develop colon cancer (from dysplasia in flat colonic mucosa).

(Choice D) Telomerase prevents the shortening of telomeres during cellular division, which extends the life of the cell. Telomerase activity is increased in many cancer types but is not especially linked to colorectal cancer.

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colorectal cancer.

(Choice C) Lynch syndrome is associated with hereditary nonpolyposis colorectal cancer due to germline mutation to one of the DNA mismatch repair genes (eg, *MSH2/6*, *MLH1*). These patients do not have extensive polyposis in the colon but are very likely to develop colon cancer (from dysplasia in flat colonic mucosa).

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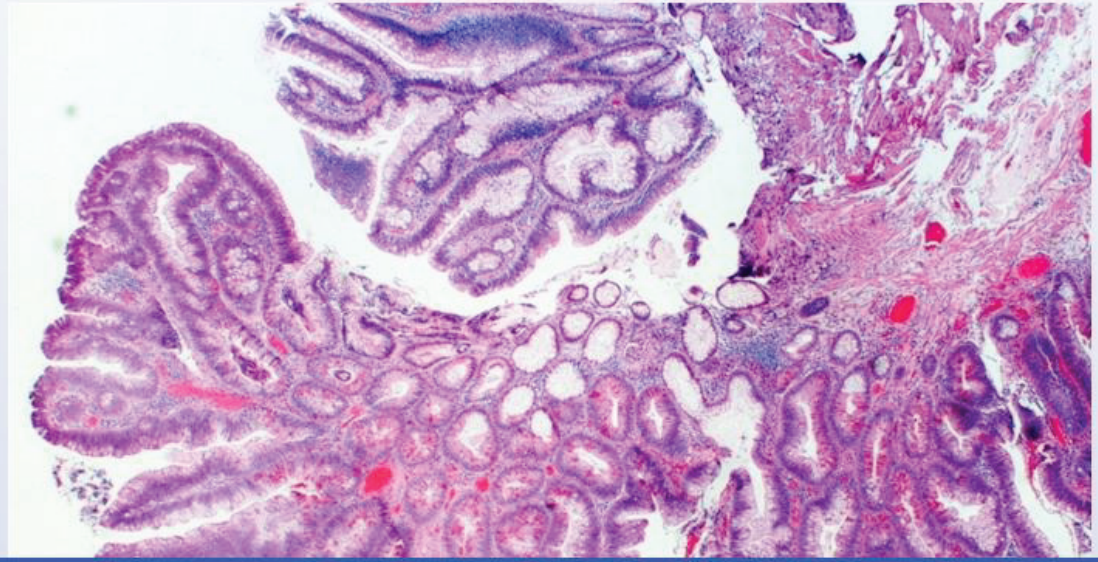
Educational objective:
Familial adenomatous polyposis is an autosomal-dominant hereditary disorder that results in the formation of innumerable colonic polyps and a nearly 100% risk of colorectal cancer. It arises due to germline mutation in the *adenomatous polyposis coli* tumor suppressor gene.

Pathology	Pathology (General Principles)	Familial adenomatous polyposis
Subject	System	Topic

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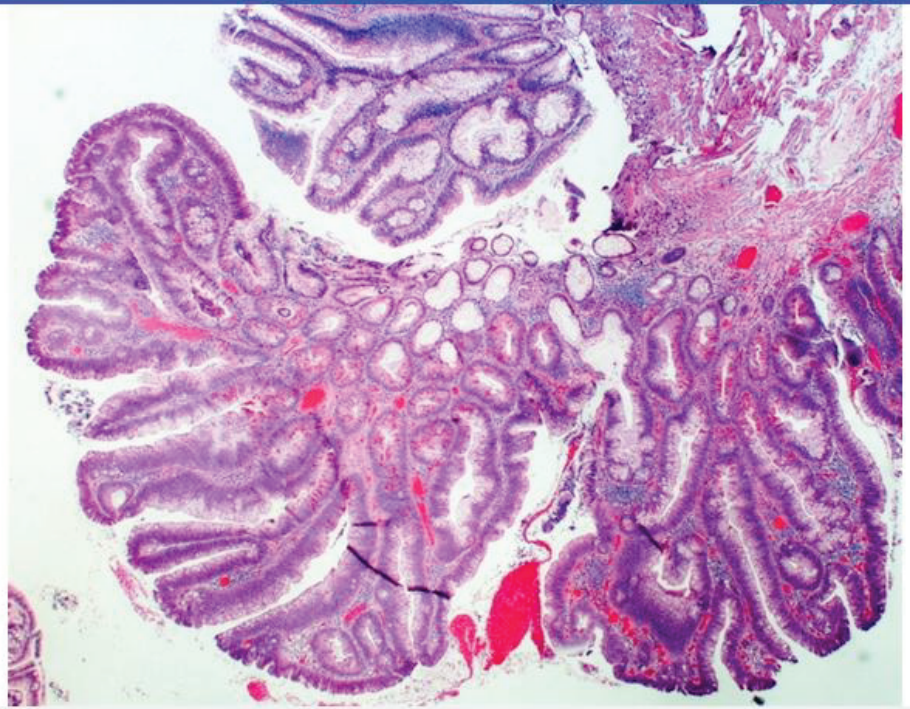
A 50-year-old man is scheduled to undergo a colonoscopy for routine colorectal cancer screening. He has no abdominal pain, gross blood in the stool, constipation, change in stool caliber, or unintentional weight loss. He also has no family history of colon cancer. The procedure is uncomplicated, but the patient is found to have a small mucosal lesion (~1 cm) in his sigmoid colon. The lesion is biopsied and its histology is shown in the image below.



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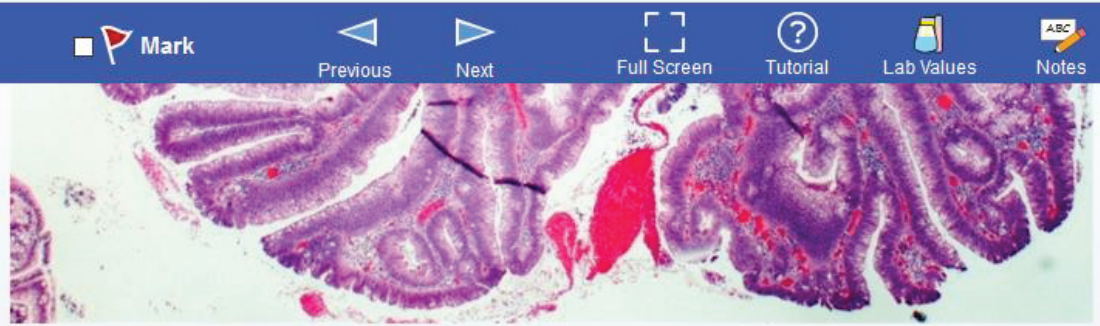
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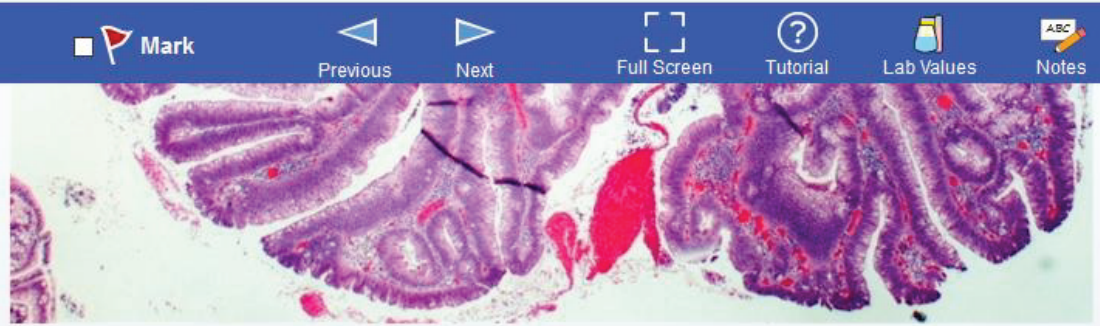
The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

- A. APC
- B. DCC
- C. K-RAS
- D. MSH2
- E. p53

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The pathogenesis of this patient's lesion most likely began with a mutation involving which of the following genes?

- A. APC (77%)
- B. DCC (2%)
- C. K-RAS (9%)
- D. MSH2 (4%)
- E. p53 (5%)

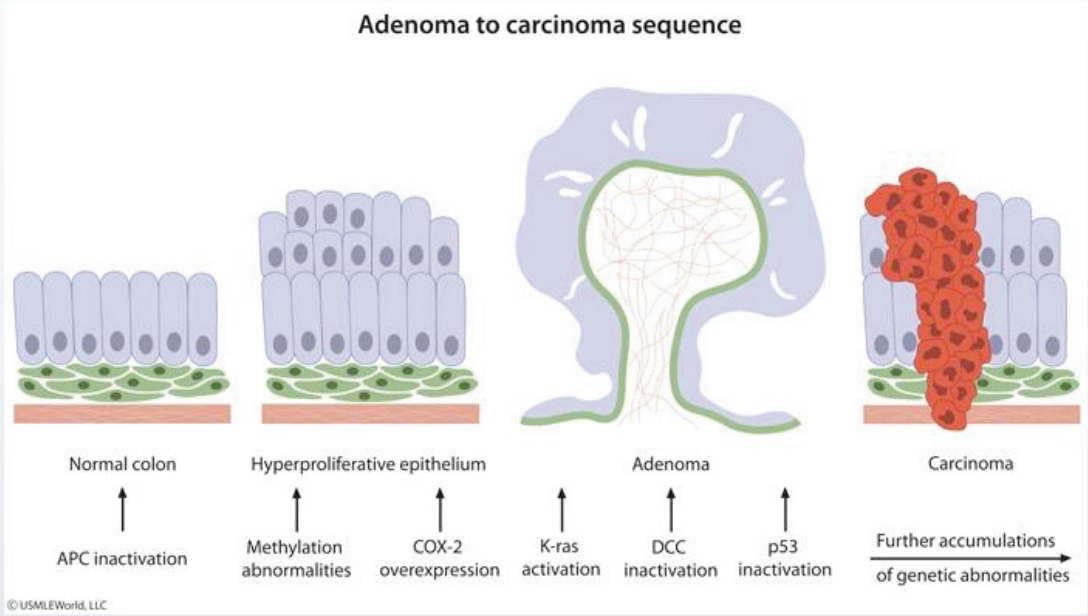
Correct

77%

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The image above shows a tubulovillous **adenomatous polyp** composed of a fibrovascular stalk with tubular glands and villous components. The glands are lined by dysplastic columnar epithelial cells that are seen in all colonic adenomatous polyps. The malignant potential of an adenomatous polyp is partly determined by the degree of dysplasia. Mildly dysplastic cells are elongated and hyperchromatic and show

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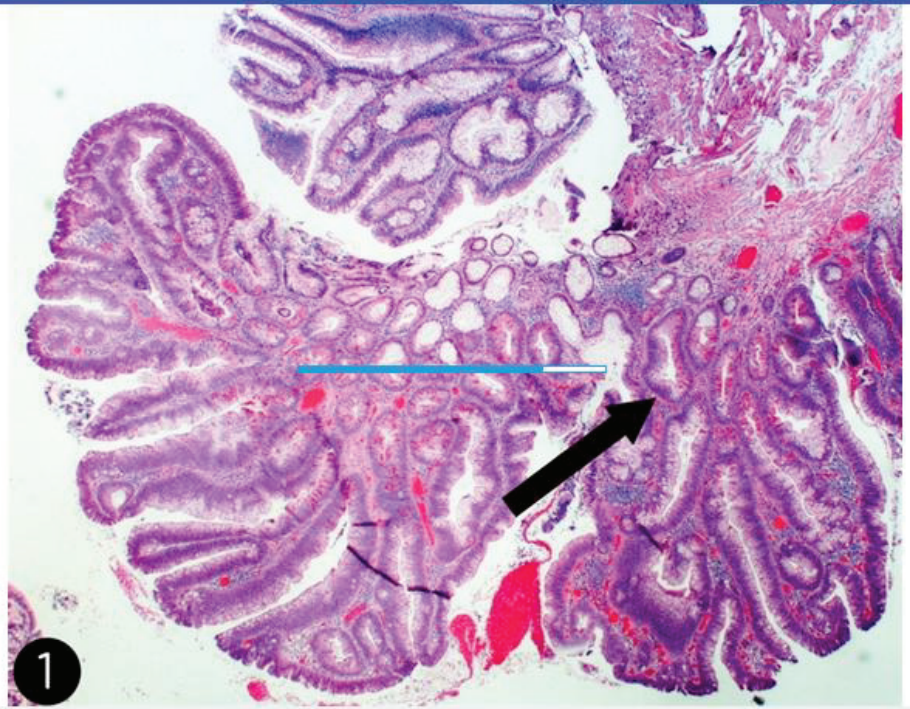
The image above shows a tubulovillous **adenomatous polyp** composed of a fibrovascular stalk with tubular glands and villous components. The glands are lined by dysplastic columnar epithelial cells that are seen in all colonic adenomatous polyps. The malignant potential of an adenomatous polyp is partly determined by the degree of dysplasia. Mildly dysplastic cells are elongated and hyperchromatic and show loss of mucin from the cytoplasm. With continued proliferation, dysplastic cells display increased variation in shape/size (pleomorphism) and the nuclei become enlarged and deeply stained (hyperchromatic). Other findings include an increase in number/size of nucleoli, nuclear-to-cytoplasmic ratio, and number of mitotic figures.

Most cases of **sporadic** colorectal carcinoma arise via the classic adenoma-to-carcinoma sequence (APC/beta-catenin pathway). The **first mutation** in this pathway usually involves the **APC tumor suppressor gene**, which is responsible for regulating cell growth/adhesion. APC gene mutation is also found in all patients with familial adenomatous polyposis. Mutations in K-RAS, DCC (Deleted in Colon Cancer), and p53 occur **later** in the adenoma-to-carcinoma sequence **(Choices B, C, and E)**. K-RAS proto-oncogene and DCC gene mutations lead to unregulated cell proliferation and avoidance of apoptosis, respectively. They are usually observed in larger adenomas (>1 cm) or carcinomas. The p53 tumor suppressor gene regulates the cell cycle and promotes repair of damaged DNA; mutations are found in

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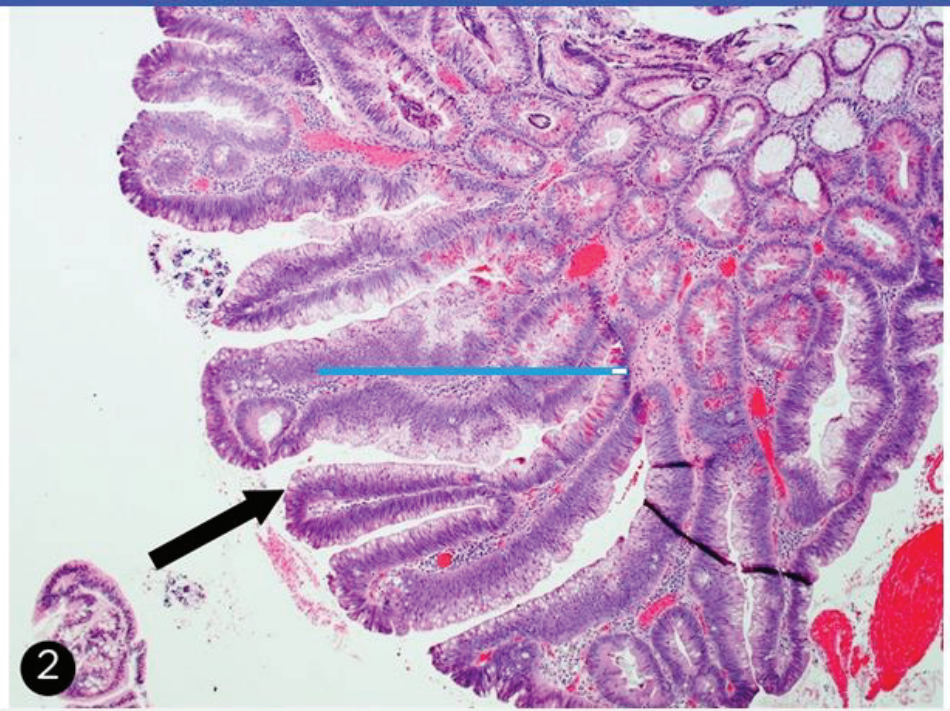


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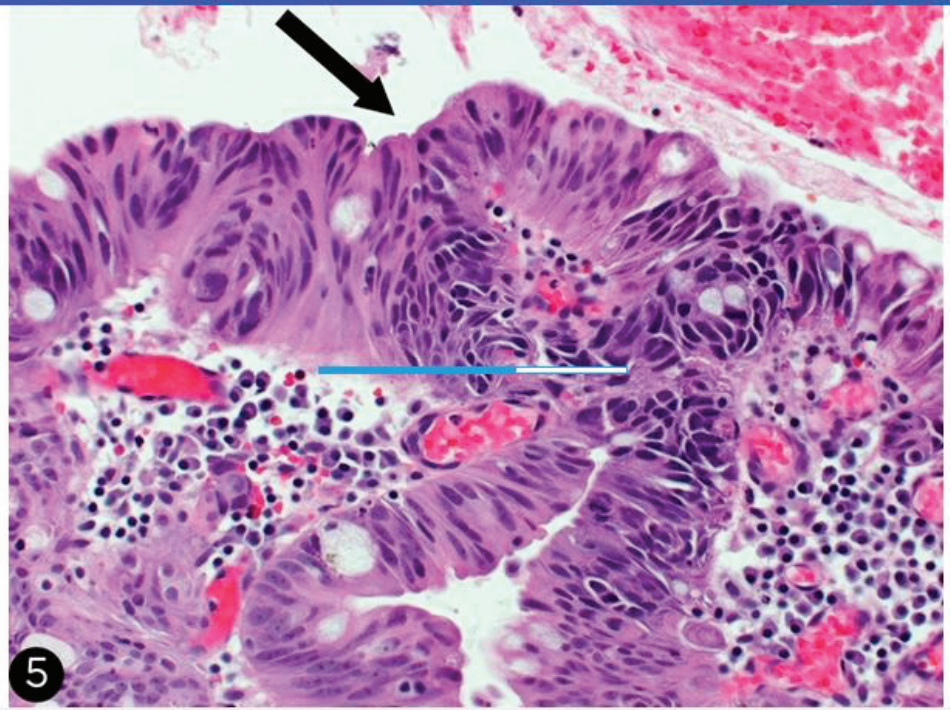


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suppressor gene regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely adenomas.

(Choice D) Mutations in DNA mismatch repair genes such as MLH1 and MSH2 result in microsatellite instability and an accumulation of genetic errors in many of the other genes implicated in colorectal carcinogenesis. Mutations in MLH1 and MSH2 cause hereditary nonpolyposis colorectal cancer (Lynch syndrome) but are not frequently associated with sporadic colorectal carcinoma.

Educational objective:

Mutation of the APC tumor suppressor gene is the first step in the classic adenoma-to-carcinoma sequence; it is found in most cases of sporadic colon cancer and in all patients with familial adenomatous polyposis. The microsatellite instability pathway is characterized by mutations in DNA mismatch repair genes and is implicated in the development of hereditary nonpolyposis colorectal cancer (Lynch syndrome).

References

- The American College of Gastroenterology Emily Couric Lecture--the adenoma-carcinoma sequence revisited: has the era of genetic tailoring finally arrived?
- Colorectal cancer: molecular features and clinical opportunities.

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A 27-year-old woman comes to the office for a health maintenance examination. The patient has no chronic medical conditions and no family history of cancer. She has had several sexual partners and takes oral contraceptives for birth control. Vital signs are normal. Physical examination, including pelvic examination, is normal. A Pap test is performed and reveals a squamous intraepithelial lesion that tests positive for human papillomavirus. A cervical biopsy is performed and reveals low-grade dysplasia. Which of the following features distinguishes this patient's lesion from cervical malignancy?

A. Abundant mitoses
B. Disordered maturation
C. Loss of cell polarity
D. Nuclear abnormalities
E. Pleomorphism
F. Reversibility of changes

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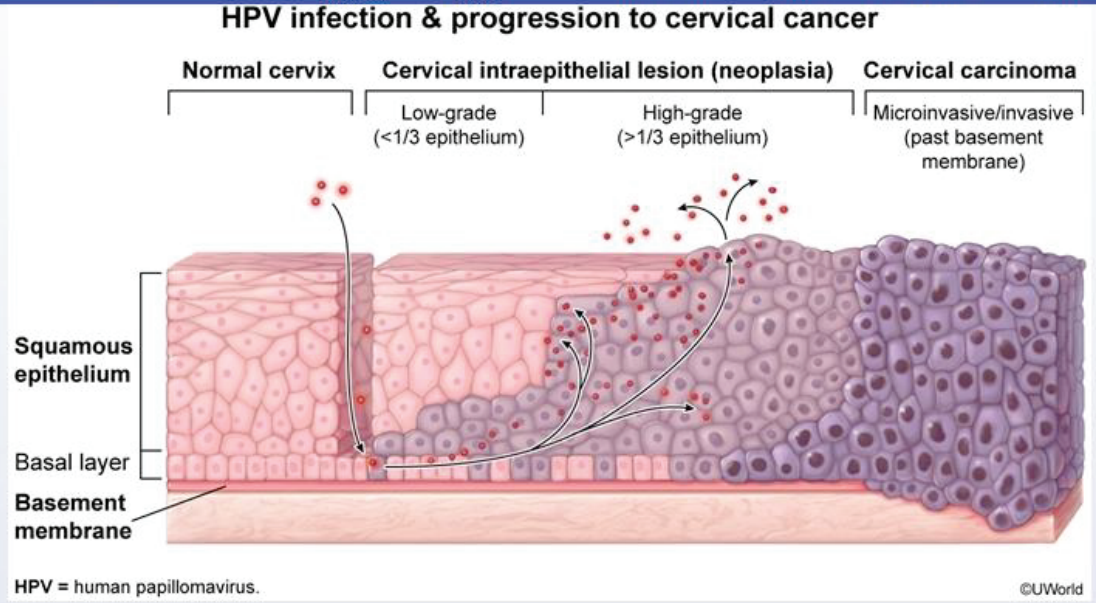
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A. Abundant mitoses (2%)
B. Disordered maturation (2%)
C. Loss of cell polarity (3%)
D. Nuclear abnormalities (2%)
E. Pleomorphism (3%)
F. Reversibility of changes (85%)

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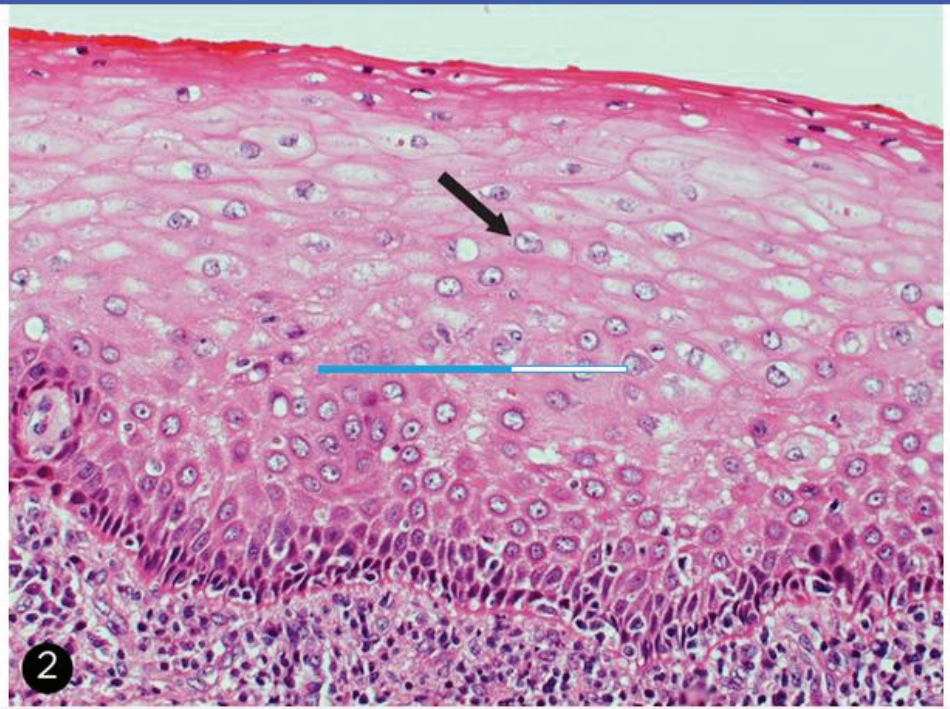
Squamous dysplasia is marked by a breakdown in the normal organized progression from tall cells in the basal layer to flattened cells on the surface. Individual cells are often pleomorphic (differing in shape and size) and also show significant abnormalities such as abundant mitotic figures and large hyperchromatic nuclei. The risk of progression to invasive carcinoma is directly linked to the degree of epithelial architecture disruption, as follows:

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HPV infection & progression to cervical cancer

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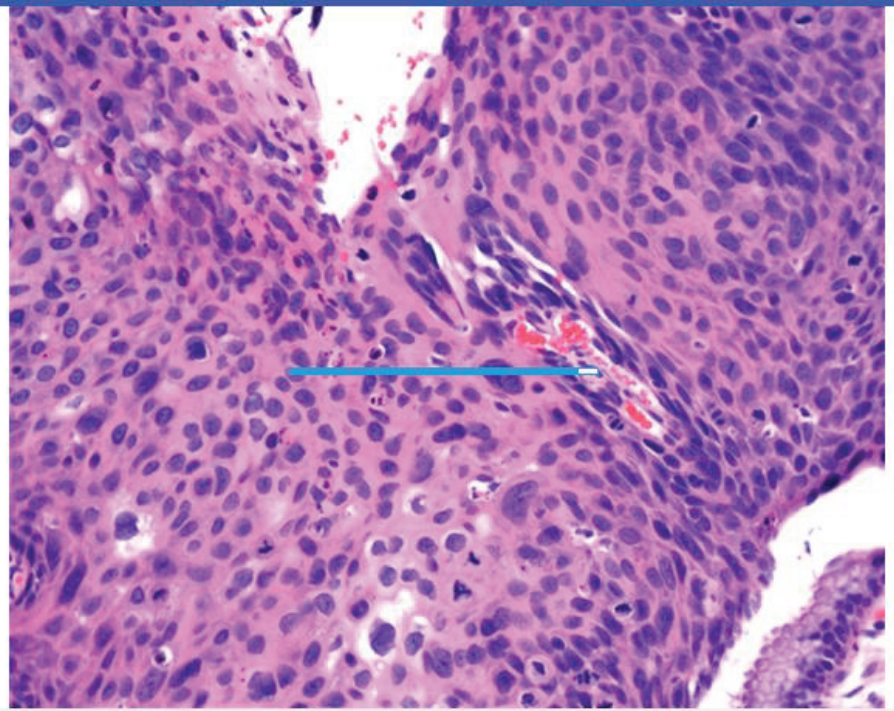
architecture disruption, as follows:

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HPV infection & progression to cervical cancer

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architecture disruption, as follows:

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architecture disruption, as follows:

- **Low-grade dysplasia** – involves only a small portion of the epithelium (typically less than one-third); it usually **spontaneously regresses** and requires no treatment.

- **High-grade dysplasia** – involves most or all of the epithelium but does not penetrate the basement membrane; it is associated with a **high risk of progression** to invasive cancer and is typically referred to as carcinoma in situ.

- **Invasive carcinoma** – involves the full thickness of the epithelium and **penetrates the basement membrane**. The malignant cells may be similar to those found in the tissue of origin (well differentiated), or may lack the characteristic features of cells found in the tissue of origin (poorly differentiated).

Cervical dysplasia is almost always due to underlying infection with oncogenic serotypes of human papilloma virus (HPV). In infected cells, viral proteins (eg, E6, E7) bind to tumor-suppressing host proteins (eg, p53) and result in their destruction by the proteasome. This eliminates a crucial check on cellular growth and can lead to dysplasia.

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Cervical dysplasia is almost always due to underlying infection with oncogenic serotypes of human papilloma virus (HPV). In infected cells, viral proteins (eg, E6, E7) bind to tumor-suppressing host proteins (eg, p53) and result in their destruction by the proteasome. This eliminates a crucial check on cellular growth and can lead to dysplasia.

(Choices A, B, C, D, and E) Abundant mitoses, disordered maturation, changes in cell polarity, nuclear abnormalities, and pleomorphism can be seen in both dysplasia and invasive carcinoma.

Educational objective:

Dysplasia is characterized by disruption of organized epithelial cell differentiation with marked cellular pleomorphism. Although high-grade dysplasia (involving most or the entire epithelial layer) often progresses to invasive cancer, low-grade dysplasia (involving a small portion of epithelium) typically spontaneously regresses. Invasive cancer occurs when the abnormal cells penetrate the basement membrane.

Pathology	Pathology (General Principles)	Cervical cancer
Subject	System	Topic

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Rats subjected to chronic inhalation exposure of formaldehyde develop nasal squamous cell carcinomas. Decreased activity of which of the following genes is likely to be found on cytogenetic studies of the tumor cells?

A. *bcr-abl*
B. *Ras*
C. *Erb-B2*
D. p53
E. N-*myc*

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Rats subjected to chronic inhalation exposure of formaldehyde develop nasal squamous cell carcinomas. Decreased activity of which of the following genes is likely to be found on cytogenetic studies of the tumor cells?

- A. *bcr-abl* (2%)
- B. *Ras* (8%)
- C. *Erb-B2* (3%)
- D. p53 (78%)
- E. N-*myc* (6%)

Incorrect
Correct answer
D

78%
Answered correctly

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Explanation

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Explanation

Decreased activity of a tumor suppressor gene would predispose to neoplasms. Of the choices listed, p53 is the only tumor suppressor gene. In normal individuals, p53 regulates cell proliferation. It acts during phase G1 of the cell cycle to detect abnormalities of the cellular genome. If there is damaged DNA, p53 will prevent the cell from progressing to mitosis, causing the cell to be arrested in the G1 phase. If the DNA can be repaired, the cell will subsequently be allowed to divide, but if the damage is so severe that repair is impossible, the cell will proceed instead to apoptosis. p53 is nicknamed "the molecular policeman" because of its important role in guarding the integrity of genetic material.

(Choice A) The *bcr-abl* fusion gene is a product of translocation of genetic material from chromosome 9 to chromosome 22 [t(9;22)]. It codes for a protein with tyrosine kinase activity. The *bcr-abl* translocation is the Philadelphia chromosome found in chronic myelogenous leukemia.

(Choice B) The *ras* proto-oncogene codes a protein that participates in signal transduction (MAP-kinase associated pathway). Over-expression of this gene leads to increased sensitivity of cells to mitogenic stimuli. This mutation occurs in a large number of cancers.

(Choice C) The *Erb-B2* gene encodes a protein with tyrosine kinase activity related to the epidermal growth factor receptor. Over-expression of this proto-oncogene is associated with breast and ovarian

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(Choice B) The *ras* proto-oncogene codes a protein that participates in signal transduction (MAP-kinase associated pathway). Over-expression of this gene leads to increased sensitivity of cells to mitogenic stimuli. This mutation occurs in a large number of cancers.

(Choice C) The *Erb-B2* gene encodes a protein with tyrosine kinase activity related to the epidermal growth factor receptor. Over-expression of this proto-oncogene is associated with breast and ovarian cancers.

(Choice E) Expression of the N-*myc* proto-oncogene is amplified in neuroblastoma.

Educational Objective:
p53 is a tumor suppressor gene that controls cell division and apoptosis. It is inactivated in many tumors.

Pathology	Pathology (General Principles)	Oncogenes and tumor suppressor genes
Subject	System	Topic

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A 65-year-old man comes to the emergency department due to acute-onset, severe right flank pain; nausea; and vomiting for the past hour. His medical conditions include prostate cancer and membranous nephropathy. Blood pressure is 148/60 mm Hg and pulse is 95/min. On physical examination, the patient appears to be in moderate distress due to pain and is diaphoretic. There is right costovertebral angle tenderness. Urinalysis shows hematuria. Contrast-enhanced CT scan reveals a wedge-shaped perfusion defect in the right kidney. The affected renal tissue is most likely to develop which of the following histologic changes over the next several days?

A. Caseous necrosis
B. Coagulative necrosis
C. Fat necrosis
D. Fibrinoid necrosis
E. Liquefactive necrosis
F. Tissue calcification

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nausea; and vomiting for the past hour. His medical conditions include prostate cancer and membranous nephropathy. Blood pressure is 148/60 mm Hg and pulse is 95/min. On physical examination, the patient appears to be in moderate distress due to pain and is diaphoretic. There is right costovertebral angle tenderness. Urinalysis shows hematuria. Contrast-enhanced CT scan reveals a wedge-shaped perfusion defect in the right kidney. The affected renal tissue is most likely to develop which of the following histologic changes over the next several days?

A. Caseous necrosis (2%)
B. Coagulative necrosis (82%)
C. Fat necrosis (0%)
D. Fibrinoid necrosis (8%)
E. Liquefactive necrosis (4%)
F. Tissue calcification (1%)

Correct

82%

53 secs

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Patterns of tissue necrosis

Type	Etiology	Morphology
Liquefactive necrosis	• Severe bacterial infections (eg, gangrene) • CNS infarcts	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ◦ Infected abscess fluid is creamy yellow due to dead leukocytes (pus) ◦ Brain infarcts resolve into CSF-filled spaces
Fibrinoid necrosis	• Hypertension • Vasculitis	• Damaged vessels leak fibrin/immune complexes • Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	• Acute pancreatitis • Trauma (subcutaneous adipose	• Free fatty acids released by active enzymes (eg, lipases) or mechanical damage

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Fat necrosis	• Acute pancreatitis • Trauma (subcutaneous adipose tissue)	• Free fatty acids released by active enzymes (eg, lipases) or mechanical damage • Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	• Mycobacterial infections • Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	• Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris • Surrounded by epithelioid macrophages & giant cells (granuloma)
Coagulative necrosis	• Irreversible ischemic injury outside CNS	• Tissue architecture is preserved due to denaturation of lytic enzymes: ◦ Cells are anucleate with eosinophilic cytoplasm ◦ Leukocytes eventually infiltrate & digest necrotic tissue

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This patient with multiple risk factors for hypercoagulability (ie, malignancy, membranous nephropathy) has flank pain, hematuria, and a **wedge-shaped** perfusion defect in the right kidney. This presentation is consistent with a **renal infarction**, likely from thromboembolic disease. Prolonged ischemia (as seen in infarcted tissue) results in irreversible cellular injury and cellular necrosis.

Necrosis is an uncontrolled process of cell death that results in denaturation of cellular proteins and enzymatic digestion of cellular components. Unlike apoptosis, necrosis leads to a loss of membrane integrity and leakage of proinflammatory intracellular material that can injure the surrounding tissue.

Necrosis occurs in several distinct morphologic patterns. In most organs, irreversible **ischemic injury** typically results in **coagulative necrosis**. Because the digestive enzymes denature before they can significantly disrupt tissue integrity, the cellular architecture is maintained but nuclei are absent. A major exception is tissue within the CNS, in which ischemia (eg, stroke) causes liquefactive necrosis with digestion of cellular constituents and liquefaction of necrotic tissue **(Choice E)**.

(Choice A) Caseous necrosis is a pattern of necrosis seen with mycobacterial or certain fungal (eg, *Histoplasma*, *Cryptococcus*) infections. Collections of epithelioid macrophages and giant cells surround white, friable, cheese-like material made up of cell fragments and proteinaceous debris (ie, caseating granulomas).

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(Choice C) Fat necrosis occurs in areas with high numbers of adipocytes (eg, pancreas, breast, subcutaneous fat) and is frequently seen in pancreatitis. Enzymes released from damaged cells break down triglycerides into free fatty acids, which combine with calcium to form soaps; anucleated adipocytes with calcium deposits are visible on microscopy.

(Choice D) Fibrinoid necrosis is a histologic pattern of injury seen in the walls of blood vessels affected by vasculitis or malignant hypertension. It results from immune complexes and/or plasma proteins (eg, fibrin) leaking through the damaged intima and depositing within the vessel wall; the deposits appear histologically as a circumferential ring of pink, amorphous material surrounding the vascular lumen.

(Choice F) Dystrophic calcification occurs in areas of tissue injury or necrosis that escape removal by phagocytes. Phosphate ions in the necrotic tissue bind calcium to form salts, which can appear grossly as white granules and microscopically as amorphous, basophilic material on hematoxylin and eosin stain. However, the calcification develops slowly over the months and years following the initial injury.

Educational objective:
Lethal tissue ischemia causes coagulative necrosis in most tissues (eg, kidney, myocardium); cellular architecture is maintained but nuclei are absent. The exception is ischemic cell death in the CNS, which causes liquefactive necrosis.

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order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 36-year-old woman comes to the office after she noticed some lumps under her arm while getting dressed. She says she feels fine and has no other symptoms. Her medical history is significant for hypothyroidism. Family history is negative. On physical examination, her body mass index is 24 kg/m^2. Breast examination shows nontender left axillary lymphadenopathy. The patient is sent for an ultrasound-guided biopsy. Microscopy of the tissue specimen shows clumps of cells that have positive immunohistochemical staining for cytokeratin.

Item 1 of 2

These cells most likely belong to which of the following lineages?

A. Epithelial
B. Lymphoid
C. Mesenchymal
D. Myeloid
E. Neuroendocrine

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hypothyroidism. Family history is negative. On physical examination, her body mass index is 24 kg/m^2. Breast examination shows nontender left axillary lymphadenopathy. The patient is sent for an ultrasound-guided biopsy. Microscopy of the tissue specimen shows clumps of cells that have positive immunohistochemical staining for cytokeratin.

Item 1 of 2

These cells most likely belong to which of the following lineages?

- A. Epithelial (84%)
- B. Lymphoid (4%)
- C. Mesenchymal (7%)
- D. Myeloid (1%)
- E. Neuroendocrine (2%)

Incorrect
Correct answer

84%
45 secs
10/14/2020

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Cytokeratins are proteins that help form the keratin-containing intermediate filaments that make up the cytoskeleton of almost all epithelial cells. Keratin proteins are highly abundant in exposed stratified squamous epithelium such as the epidermis and oral mucosa and are less abundant but still present in simple epithelium such as that found in the liver, gut, and pancreas. As a result, cytokeratin is a commonly used immunohistochemical **marker for epithelial-derived tumors**, such as breast cancer. Keratin is also the major protein component of hair and nails.

Keratin is composed of large amounts of alanine and glycine that, because of their small structure, are able to coil tightly and form large numbers of hydrogen bonds. In addition, keratin contains a significant amount of the sulfur-containing amino acid cysteine, and formation of disulfide bonds between cysteine residues gives additional rigidity and toughness to the protein.

(Choice B) CD20 is a marker used to identify B lymphocytes, and CD3 is used to identify T lymphocytes.

(Choice C) Vimentin is an intermediate filament present in mesenchymal tissue and can be used to detect sarcomas.

(Choice D) Myeloperoxidase is a peroxidase enzyme that can be used as a marker for myeloid cells such as those in acute myeloid leukemia.

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(Choice C) Vimentin is an intermediate filament present in mesenchymal tissue and can be used to detect sarcomas.

(Choice D) Myeloperoxidase is a peroxidase enzyme that can be used as a marker for myeloid cells such as those in acute myeloid leukemia.

(Choice E) Chromogranin A and synaptophysin are markers used for neuroendocrine tumors.

Educational objective:
Cytokeratin is a commonly used immunohistochemical marker of epithelial cell carcinomas.

References

- Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.

Pathology Pathology (General Principles) Breast cancer

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Item 2 of 2

The cells identified by the special immunohistochemical stain are shown to overexpress a 185 kD glycoprotein that spans the cell membrane and has tyrosine kinase activity in the intracellular domain. Which of the following is the most likely function of this protein?

A. Accelerates cell proliferation
B. Acts as a sex hormone receptor
C. Governs intercellular binding
D. Induces cytokine release
E. Mediates endocytosis

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Item 2 of 2

The cells identified by the special immunohistochemical stain are shown to overexpress a 185 kD glycoprotein that spans the cell membrane and has tyrosine kinase activity in the intracellular domain. Which of the following is the most likely function of this protein?

- A. Accelerates cell proliferation (68%)
- B. ~~Acts as a sex hormone receptor~~ (11%)
- C. Governs intercellular binding (9%)
- D. ~~Induces cytokine release~~ (8%)
- E. ~~Mediates endocytosis~~ (2%)

Correct

68%
Answered correctly

49 secs
Time Spent

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The **HER2 oncogene** codes for a human epidermal growth factor receptor with tyrosine kinase activity in the intracellular domain. It is known to play a role in the activation of transduction pathways that control epithelial growth and differentiation. Epithelial cell carcinomas that overexpress HER2 demonstrate **increased proliferation** and resistance to apoptosis. Consequently, HER2-positive breast cancers have a higher risk of disease recurrence and **worse prognosis** compared to HER2-negative breast cancers. **Trastuzumab** (a monoclonal antibody against HER2) is used to treat women who test positive for overexpression of the HER2 oncogene.

(Choice B) Estrogen and progesterone receptors are intracellular receptors that are frequently overexpressed in patients with breast cancer. Stimulation of these hormone receptors increases cellular proliferation, and patients with hormone-receptor-positive breast cancer are treated with antiestrogen medications to suppress tumor growth.

(Choice C) Intercellular binding is mediated by cell surface proteins such as intercellular adhesion molecules (ICAMs), selectins, and numerous others. Many adhesion proteins, including ICAMS, also play a role in signal transduction.

(Choice D) Various hormones, cytokines, and other stimuli can induce cytokine release from a number of cell types. One example of a receptor that induces cytokine release is the Toll-like receptor, which detects

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medications to suppress tumor growth.

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(Choice D) Various hormones, cytokines, and other stimuli can induce cytokine release from a number of cell types. One example of a receptor that induces cytokine release is the Toll-like receptor, which detects conserved microbial molecular structures.

(Choice E) Clathrin is an intracellular protein that helps form rounded vesicles in the cytoplasm. Clathrin-coated vesicles help mediate intracellular trafficking and endocytosis.

Educational objective:
The HER2 oncogene encodes for a transmembrane glycoprotein with intrinsic tyrosine kinase activity and is a member of the family of epidermal growth factor receptors. Overexpression of this protein is associated with a worse prognosis and increased risk of disease recurrence.

References

- Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues.

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A 53-year-old man comes to the emergency department due to severe heartburn and difficulty swallowing for the last few weeks. He has had mild to moderate heartburn for several years and has tried weight loss, elevating the head of his bed while sleeping, and several months of proton pump inhibitor therapy. Other medical problems include hypertension and hypothyroidism. Temperature is 36.7 C (98.1 F), blood pressure is 130/80 mm Hg, pulse is 78/min, and respirations are 16/min. BMI is 25 kg/m^2. Physical examination is unremarkable. An upper gastrointestinal endoscopy is performed, and esophageal biopsy shows columnar epithelium with interspersed goblet cells. A similar adaptive response can be seen in which of the following scenarios?

A. Bronchial epithelial cells in a chronic cigarette smoker
B. Epidermal cells in a patient with psoriasis
C. Melanocytes in a large, irregular mole
D. Myocardial cells in a patient with aortic stenosis
E. Skeletal myocytes after prolonged immobility

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- A. Bronchial epithelial cells in a chronic cigarette smoker (94%)
- B. Epidermal cells in a patient with psoriasis (1%)
- C. Melanocytes in a large, irregular mole (1%)
- D. Myocardial cells in a patient with aortic stenosis (0%)
- E. Skeletal myocytes after prolonged immobility (0%)

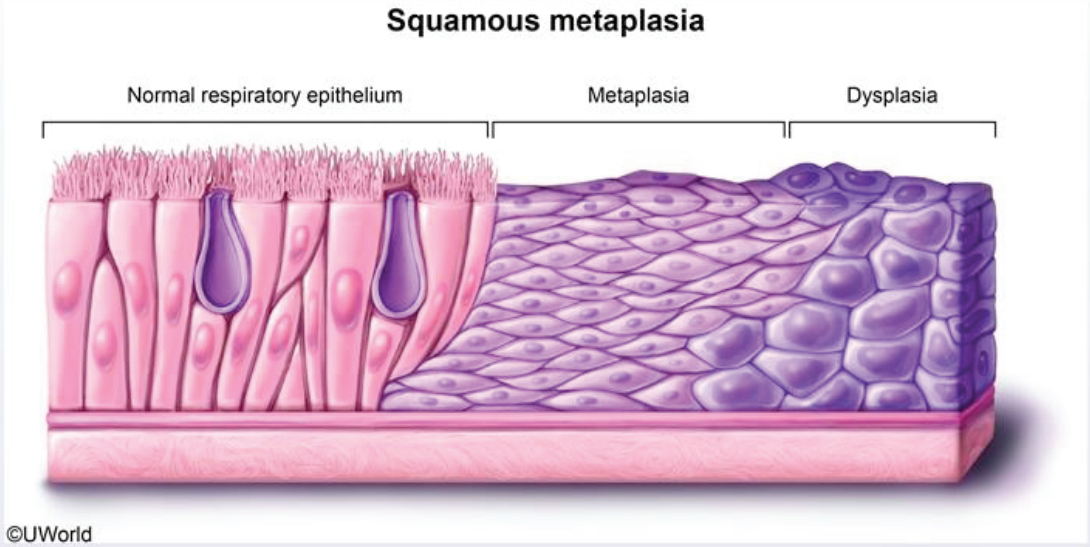
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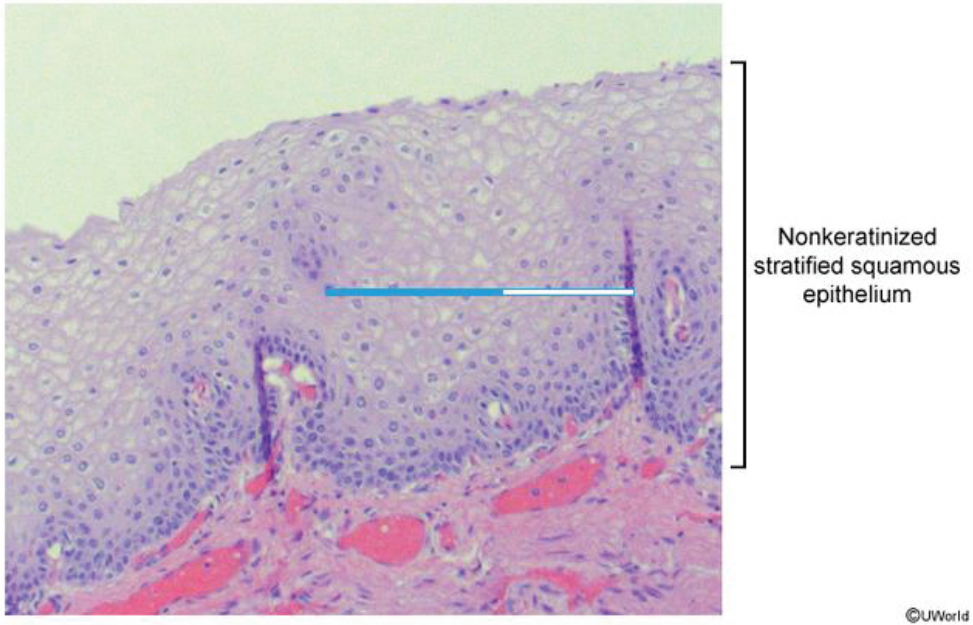
The esophagus is normally lined by nonkeratinized, stratified squamous epithelium. However, chronic exposure to acidic stomach contents can damage the epithelial surface and result in the release of cytokines and growth factors that cause esophageal stem cells to **differentiate** into an **alternate epithelial cell type** (intestine-like columnar cells) better suited for an acidic environment. The substitution of one differentiated epithelial cell type for another in response to adverse environmental conditions is called

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Normal esophagus



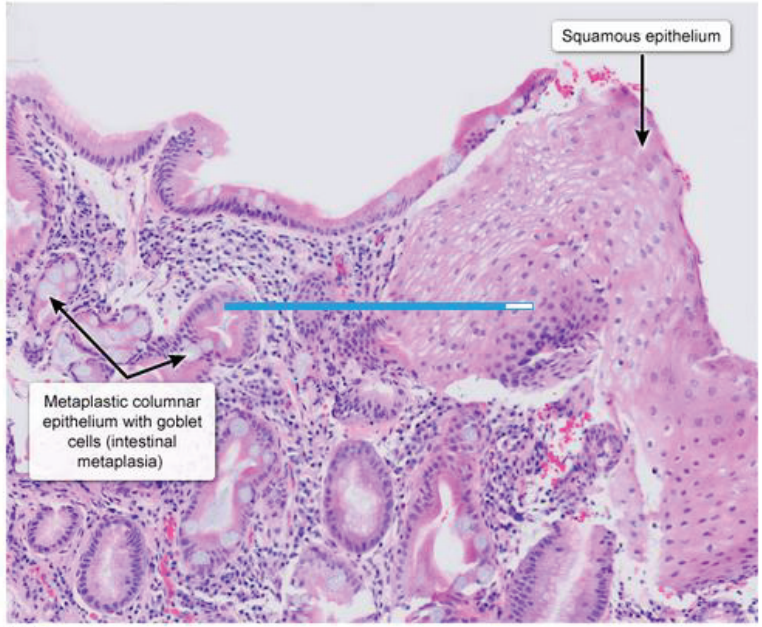
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Exhibit Display

Barrett esophagus



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cell type (intestine-like columnar cells) better suited for an acidic environment. The substitution of one differentiated epithelial cell type for another in response to adverse environmental conditions is called **metaplasia**.

Metaplasia is also seen in the trachea and **bronchi of chronic cigarette smokers** where the irritative effect of smoke leads to the replacement of normal ciliated columnar cells with heartier stratified squamous epithelium. Although this substitution reduces epithelial injury, it also eliminates the cell types that contain cilia and produce mucus, which increases the risk of respiratory infection.

Metaplasia is a reversible condition, but continued environmental stress can lead to **malignant transformation** (metaplasia → dysplasia → invasive cancer). For instance, the metaplasia seen in the distal esophagus in response to chronic acid exposure (Barrett esophagus) is associated with a high risk of malignant transformation into esophageal adenocarcinoma.

(Choice B) Psoriasis is characterized by hyperplasia, an increase in the number of cells within a tissue due to hormones or growth factors. Histology will show hyperproliferation of the dermis with epidermal thickening (acanthosis) and prolonged downward thickenings between dermal papillae ("rete ridges").

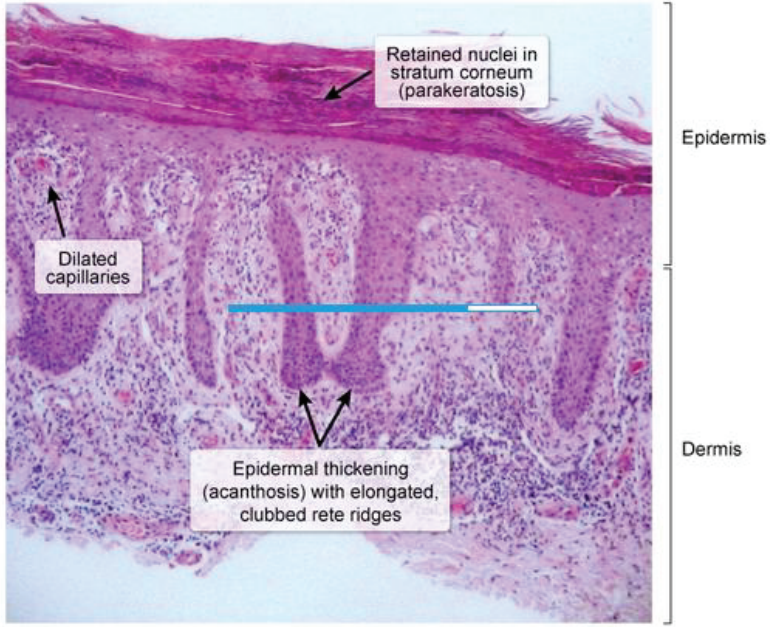
(Choice C) Irregular moles (eg, melanoma, atypical mole) are likely to contain dysplastic cells. Dysplasia is characterized by abnormal epithelial cellular architecture and irregular cellular growth. In metaplasia

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Psoriasis



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thickening (acanthosis) and prolonged downward thickenings between dermal papillae ("rete ridges").

(Choice C) Irregular moles (eg, melanoma, atypical mole) are likely to contain dysplastic cells. Dysplasia is characterized by abnormal epithelial cellular architecture and irregular cellular growth. In metaplasia, one mature, differentiated cell type is replaced by another.

(Choice D) Hypertrophy is an increase in the size, but not number, of cells. Left ventricular hypertrophy can occur with aortic stenosis due to higher systolic pressures necessitating increased myocardial effort.

(Choice E) Atrophy is a reduction in cell size and number; it can occur in skeletal muscles following a period of immobility (eg, bedbound patient).

Educational objective:

Metaplasia is the substitution of one differentiated cell type for another due to the presence of an adverse environmental stimulus. It is often seen in the bronchi of chronic cigarette smokers (substitution of ciliated columnar epithelium with stratified squamous cells) and the distal esophagus of patients with chronic gastroesophageal reflux (substitution of stratified squamous epithelium with intestinal columnar cells). Metaplasia can lead to subsequent dysplasia and malignant transformation.

References

- Common questions about Barrett esophagus.

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"Moldy" grains in some regions of China contain a substance that causes a specific G-to-T mutation in gene p53. The population in these regions is expected to be at an increased risk of which of the following diseases?

A. Lung cancer
B. Infectious diarrhea
C. Dilated cardiomyopathy
D. Liver cancer
E. Congenital heart defects
F. Hypothyroidism
G. Osteoporosis
H. Pancreatic cancer

Submit

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"Moldy" grains in some regions of China contain a substance that causes a specific G-to-T mutation in gene p53. The population in these regions is expected to be at an increased risk of which of the following diseases?

A. Lung cancer (16%)
B. ~~Infectious diarrhea~~ (2%)
C. ~~Dilated cardiomyopathy~~ (0%)
✓ D. Liver cancer (64%)
E. ~~Congenital heart defects~~ (0%)
F. ~~Hypothyroidism~~ (0%)
G. ~~Osteoporosis~~ (1%)
✗ H. Pancreatic cancer (13%)

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When the humidity and temperature are favorable, specific strains of the fungi *Aspergillus flavus* and *Aspergillus parasiticus* grow on foods such as corn, soybeans, and peanuts, producing aflatoxins as a byproduct. These aflatoxins are categorized as A1, B2, G1, and G2, with aflatoxin B1 the most common and most toxic.

High levels of dietary aflatoxin intake have been strongly associated with hepatocellular carcinoma. In certain areas within Asia and Africa where aflatoxin B1 exposure is high, p53 mutations have been identified in most individuals who developed hepatocellular carcinoma. More than 90% of these aflatoxin-induced p53 mutations are a classic G:C → T:A transversion in codon 249. In addition, research suggests that the combination of chronic aflatoxin exposure and hepatitis B infection significantly increases the risk of developing hepatocellular carcinoma.

(Choices A, B, C, E, F, G, and H) Lung cancer, infectious diarrhea, dilated cardiomyopathy, congenital heart defects, hypothyroidism, osteoporosis, and pancreatic cancer are not associated with aflatoxin-induced mutation of the p53 gene.

Educational Objective:

High levels of dietary aflatoxin exposure is associated with a G:C → T:A transversion in codon 249 of the

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High levels of dietary aflatoxin intake have been strongly associated with hepatocellular carcinoma. In certain areas within Asia and Africa where aflatoxin B1 exposure is high, p53 mutations have been identified in most individuals who developed hepatocellular carcinoma. More than 90% of these aflatoxin-induced p53 mutations are a classic G:C → T:A transversion in codon 249. In addition, research suggests that the combination of chronic aflatoxin exposure and hepatitis B infection significantly increases the risk of developing hepatocellular carcinoma.

(Choices A, B, C, E, F, G, and H) Lung cancer, infectious diarrhea, dilated cardiomyopathy, congenital heart defects, hypothyroidism, osteoporosis, and pancreatic cancer are not associated with aflatoxin-induced mutation of the p53 gene.

Educational Objective:
High levels of dietary aflatoxin exposure is associated with a G:C → T:A transversion in codon 249 of the p53 gene, a mutation thought to greatly increase the risk of developing hepatocellular carcinoma.

Pathology	Pathology (General Principles)	Hepatocellular cancer
Subject	System	Topic

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A 73-year-old man comes to the emergency department due to right-sided weakness and difficulty speaking. The patient woke up with the symptoms an hour before arriving but felt well when he went to bed last night. He has a history of paroxysmal atrial fibrillation but is not adherent with medical therapy. Temperature is 98.6 F (37 C), blood pressure is 130/70 mm Hg, and pulse is 110/min and irregularly irregular. Physical examination shows right-sided hemiplegia, hemisensory loss, and aphasia. Despite appropriate treatment, the patient's symptoms fail to improve. Over the next week, which of the following processes is most likely to occur in the affected brain region?

A. Accumulation of fibrin-like material in vessel walls

B. Formation of a necrotic focus surrounded by epithelioid macrophages

C. Deposition of fatty acid and calcium complexes

D. Hydrolytic enzyme-induced tissue digestion

E. Tissue necrosis with preservation of cellular architecture

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A. Accumulation of fibrin-like material in vessel walls (3%)
B. Formation of a necrotic focus surrounded by epithelioid macrophages (16%)
C. Deposition of fatty acid and calcium complexes (1%)
D. Hydrolytic enzyme-induced tissue digestion (70%)
E. Tissue necrosis with preservation of cellular architecture (7%)

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Patterns of tissue necrosis

Type	Etiology	Morphology
Liquefactive necrosis	• Severe bacterial infections (eg, gangrene) • CNS infarcts	• Necrotic tissue is digested by hydrolytic enzymes into a viscous fluid: ◦ Infected abscess fluid is creamy yellow due to dead leukocytes (pus) ◦ Brain infarcts resolve into CSF-filled spaces
Fibrinoid necrosis	• Hypertension • Vasculitis	• Damaged vessels leak fibrin/immune complexes • Eosinophilic layer of proteinaceous material in vessel walls
Fat necrosis	• Acute pancreatitis	• Free fatty acids released by active enzymes (eg, lipases) or mechanical

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Fat necrosis	• Acute pancreatitis • Trauma (subcutaneous adipose tissue)	• Free fatty acids released by active enzymes (eg, lipases) or mechanical damage • Fatty acids combine with calcium, forming chalky-white deposits (saponification)
Caseous necrosis	• Mycobacterial infections • Fungal infections (eg, *Histoplasma*, *Cryptococcus*, *Coccidioides*)	• Friable, cheeselike material composed of cell fragments & amorphous proteinaceous debris • Surrounded by epithelioid macrophages & giant cells (granuloma)
Coagulative necrosis	• Irreversible ischemic injury outside CNS	• Tissue architecture is preserved due to denaturation of lytic enzymes: ◦ Cells are anucleate with eosinophilic cytoplasm ◦ Leukocytes eventually infiltrate & digest necrotic tissue

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This patient's symptoms are consistent with an **ischemic stroke** involving the left middle cerebral artery territory. An **embolism** is the most likely cause given his history of atrial fibrillation in the absence of anticoagulation therapy. The resulting irreversible neural cell injury initiates immune cell migration and **hydrolytic enzyme release**, leading to necrosis of damaged neural tissue. Although ischemic cell death in most organs results in coagulative necrosis, in the brain such injury causes **liquefactive necrosis** within 10 days of the infarction due to the brain's lack of supporting architecture.

The infarcted CNS tissue is then digested by microglia and replaced with a cystic space surrounded by a dense astroglial scar (gliosis) over the ensuing months to years.

(Choice A) Fibrinoid necrosis is a pattern of injury that results in accumulation of fibrin-like material in the walls of blood vessels affected by vasculitis syndromes (eg, polyarteritis nodosa) or malignant hypertension. Although fibrinoid necrosis in cerebral arteries can predispose a patient to hemorrhagic stroke, this change would not be an expected complication of acute ischemic stroke.

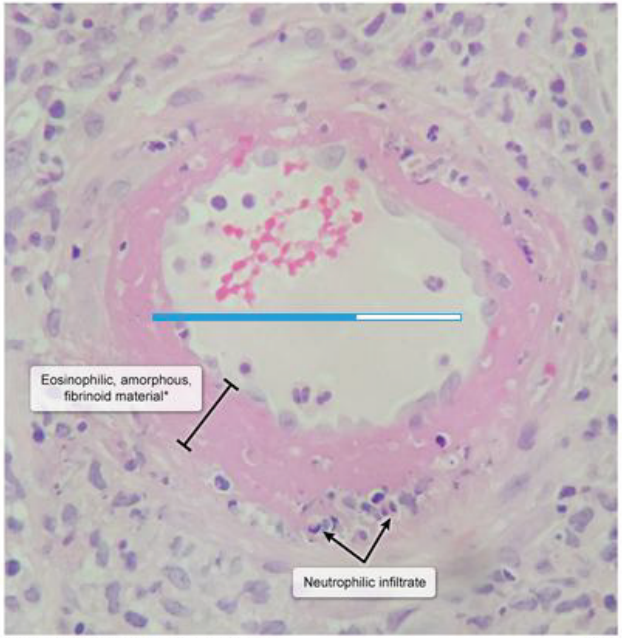
(Choice B) Focal tuberculous infection can occur in the CNS and cause granulomas with caseous necrosis (epithelioid macrophages around a necrotic focus) within the affected parenchyma. However, the onset of neurologic symptoms in patients with tuberculous brain abscesses tends to be more chronic and progressive than this patient's acute presentation.

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Fibrinoid necrosis



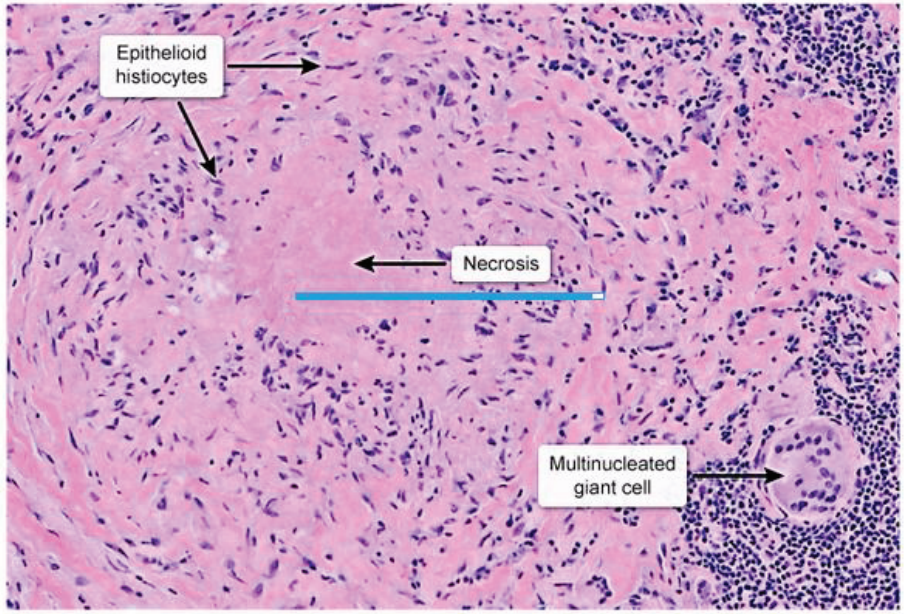
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Exhibit Display

Caseating granuloma



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progressive than this patient's acute presentation.

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necrosis (epithelioid macrophages around a necrotic focus) within the affected parenchyma. However, the onset of neurologic symptoms in patients with tuberculous brain abscesses tends to be more chronic and progressive than this patient's acute presentation.

(Choice C) Breakdown of adipose tissue (ie, fat necrosis) due to mechanical trauma or pancreatic enzyme release (eg, acute pancreatitis) is characterized by infiltrating foamy macrophages containing engulfed lipid debris and release of free fatty acids that combine with calcium to form basophilic deposits.

(Choice E) Coagulative necrosis occurs following hypoxic cell death in all tissues except the CNS. It results in the acute denaturation of structural and enzymatic cellular proteins. Cell nuclei disappear, but the basic architecture of the affected tissue is preserved because intracellular proteolytic enzymes are inactivated during the injury process.

Educational objective:
Irreversible ischemic injury to brain tissue causes tissue digestion by hydrolytic enzymes (liquefactive necrosis). The infarcted CNS tissue is eventually replaced with a cystic astroglial scar. In other organs, lethal ischemic injury results in coagulative necrosis.

Pathology	Pathology (General Principles)	Necrosis
Subject	System	Topic

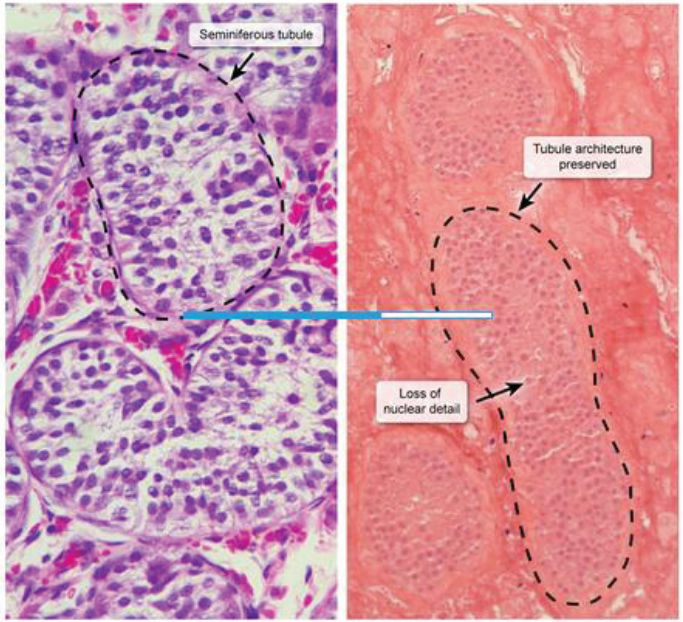
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necrosis (epithelioid macrophages around a necrotic focus) within the affected parenchyma. However, the

Exhibit Display

Coagulative necrosis



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Subject System Topic

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A 61-year-old man comes to the emergency department due to fever, chills, and a productive cough with thick, blood-tinged sputum for the past several days. His temperature is 38.8 C (102 F), blood pressure is 90/60 mm Hg, and pulse is 110/min. On examination, the patient is lethargic and ill appearing. Bronchial breath sounds and crackles are present in the right lung. Blood and sputum cultures grow *Klebsiella pneumoniae*. It is determined that the bacteria express a lipopolysaccharide on their outer membrane surface that stimulates toll-like receptors in the inflammatory cells. This in turn leads to degradation of the IκB inhibitor protein, which normally binds to a latent transcription factor found in the cytoplasm. Which of the following factors is most likely to be directly activated by the removal of this inhibitor protein?

A. Granulocyte colony-stimulating factor
B. Janus kinase 2
C. Nuclear factor-kappa B
D. Transforming growth factor-β
E. Tumor necrosis factor-α

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thick, blood-tinged sputum for the past several days. His temperature is 38.8 C (102 F), blood pressure is 90/60 mm Hg, and pulse is 110/min. On examination, the patient is lethargic and ill appearing. Bronchial breath sounds and crackles are present in the right lung. Blood and sputum cultures grow *Klebsiella pneumoniae*. It is determined that the bacteria express a lipopolysaccharide on their outer membrane surface that stimulates toll-like receptors in the inflammatory cells. This in turn leads to degradation of the IκB inhibitor protein, which normally binds to a latent transcription factor found in the cytoplasm. Which of the following factors is most likely to be directly activated by the removal of this inhibitor protein?

A. Granulocyte colony-stimulating factor (3%)
B. Janus kinase 2 (6%)
C. Nuclear factor-kappa B (67%)
D. Transforming growth factor-β (4%)
E. Tumor necrosis factor-α (18%)

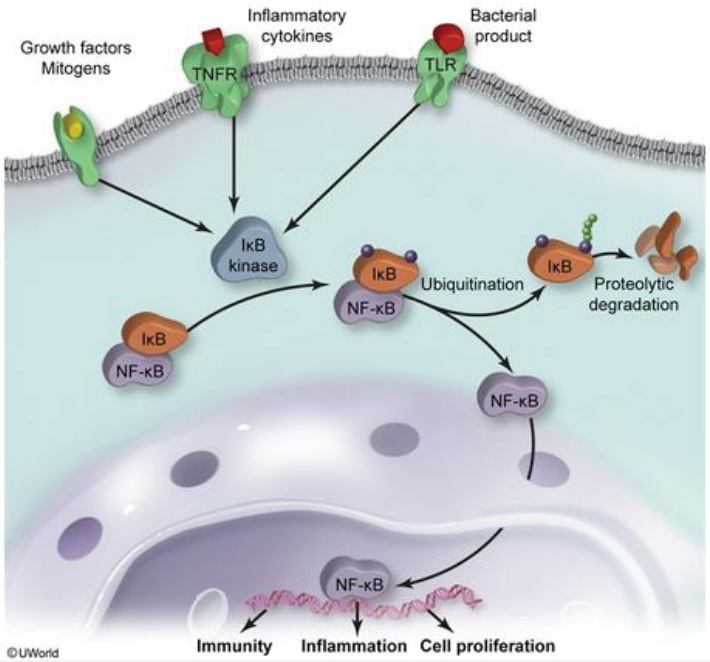
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Nuclear factor kappa B signaling



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Nuclear factor-kappa B (NF-κB) is part of a family of **transcription factors** that perform a critical role in the immune response to infection and inflammation. In inflammatory cells, NF-κB is normally present in a latent, inactive state bound to its inhibitor protein, IκB. As part of the classical activation pathway, an extracellular signal, such as the binding of bacterial antigens to a toll-like receptor, causes activation of **IκB kinase**. This results in **ubiquitination** and subsequent destruction of IκB with the release of free NF-κB. Once free, NF-κB enters the nucleus and promotes the synthesis of a number of **inflammatory proteins** such as cytokines, acute phase reactants, cell adhesion molecules, and leukocyte-related growth factors. The inflammatory cascade is self-limiting as NF-κB also stimulates the transcription of more IκB, ultimately rebinding the freed NF-κB.

(Choices A and E) Granulocyte colony-stimulating factor (G-CSF) is the principal protein that stimulates the production and release of neutrophils from the bone marrow. Tumor necrosis factor-α (TNF-α) plays a major role in the response to infection by increasing neutrophil chemotaxis and stimulating macrophage phagocytosis. Although NF-κB upregulates transcription of G-CSF and TNF-α, IκB degradation is not directly involved in the activation of these factors.

(Choice B) Janus kinase 2 (JAK2) is a tyrosine kinase involved in the signaling pathway for myeloproliferation. Constituent activation of JAK2 is associated with polycythemia vera, essential thrombocytosis, and myelofibrosis. It does not play a major role in the immune response to infection

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phagocytosis. Although NF-κB upregulates transcription of G-CSF and TNF-α, IκB degradation is not directly involved in the activation of these factors.

(Choice B) Janus kinase 2 (JAK2) is a tyrosine kinase involved in the signaling pathway for myeloproliferation. Constituent activation of JAK2 is associated with polycythemia vera, essential thrombocytosis, and myelofibrosis. It does not play a major role in the immune response to infection.

(Choice D) Although transforming growth factor-β (TGF-β) also has a role in the immune response and is triggered by inflammatory pathways, it is complexed to TGF-β binding protein and latency-associated peptide, not IκB.

Educational objective:

Nuclear factor-kappa B (NF-κB) is a transcription factor with a critical role in the immune response to infection. NF-κB is normally present in the cytoplasm in a latent, inactive state bound to its inhibitor protein, IκB. Extracellular substances such as lipopolysaccharide can initiate a signal cascade that results in the destruction of IκB and translocation of free NF-κB to the nucleus.

References

- The nuclear factor NF-?B pathway in inflammation.
- Regulation and function of NF-kappaB transcription factors in the immune system

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A 74-year-old woman comes to the emergency department due to 2 days of left leg pain and numbness. She has a history of atrial fibrillation and hypertension. Her left lower limb is pale and cold to palpation below the knee. Arterial Doppler ultrasound shows an occluding thrombus, and a left femoral embolectomy is performed. Post-procedure dorsalis pedis and posterior tibial pulses become palpable. Several hours later, the patient begins to experience severe left calf pain. On repeat examination, the left calf is swollen, tense, and tender, and the pain worsens with dorsiflexion of the left foot. The distal pulses are also absent. The physician suspects injury of the reperfused muscles in part due to overproduction of reactive oxygen species. Which of the following enzymes is most likely to help neutralize these toxic molecules?

A. Cytochrome oxidase
B. Cytochrome P450
C. Myeloperoxidase
D. NADPH oxidase
E. Superoxide dismutase

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She has a history of atrial fibrillation and hypertension. Her left lower limb is pale and cold to palpation below the knee. Arterial Doppler ultrasound shows an occluding thrombus, and a left femoral embolectomy is performed. Post-procedure dorsalis pedis and posterior tibial pulses become palpable. Several hours later, the patient begins to experience severe left calf pain. On repeat examination, the left calf is swollen, tense, and tender, and the pain worsens with dorsiflexion of the left foot. The distal pulses are also absent. The physician suspects injury of the reperfused muscles in part due to overproduction of reactive oxygen species. Which of the following enzymes is most likely to help neutralize these toxic molecules?

- A. Cytochrome oxidase (4%)
- B. Cytochrome P450 (3%)
- C. Myeloperoxidase (6%)
- ✗ D. NADPH oxidase (17%)
- ✓ E. Superoxide dismutase (67%)

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Correct answer

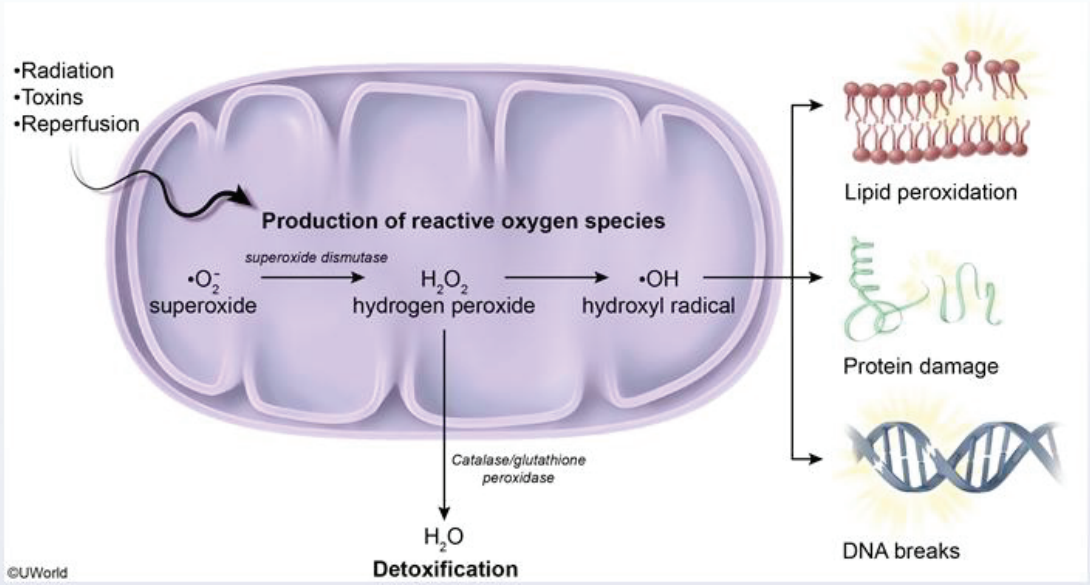
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The vignette describes **acute compartment syndrome** secondary to reperfusion injury. Restoration of arterial blood flow to an affected limb floods ischemic tissue with oxygen. Molecular oxygen reacts with xanthine oxidase, NADPH oxidase, and nitric oxide synthase to form **reactive oxygen species (ROS)** such as superoxide, hydroxyl radicals, and singlet oxygen. ROS disrupt cellular functions leading to DNA mutations, protein synthesis disruption, and membrane lipid peroxidation

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mutations, protein synthesis disruption, and membrane lipid peroxidation.

Antioxidant enzymes, such as **superoxide dismutase, glutathione peroxidase**, **and catalase**, convert ROS to oxygen and water, neutralizing their capacity for cellular damage. ROS generated during cellular respiration are typically neutralized by antioxidants before they become problematic. However, in the **postischemic state**, the production of ROS exceeds the neutralizing capabilities of antioxidant enzymes (**high oxidative stress**), leading to increased cell injury and death.

(Choice A) Cytochrome oxidase is the final component of the electron transport chain and functions to convert molecular oxygen to water while establishing the proton gradient necessary for synthesis of ATP.

(Choice B) Cytochrome P450 enzymes metabolize endogenous toxins as well as drugs. They are capable of producing reactive oxygen species, which can contribute to the hepatotoxicity seen with certain drugs.

(Choice C) Myeloperoxidase is found in neutrophils and converts hydrogen peroxide to hypochlorous acid, a bactericidal compound that also causes oxidative damage to host cells.

(Choice D) NADPH oxidase catalyzes the reduction of molecular oxygen to superoxide free radicals, aiding in bacterial destruction by phagocytic cells. Deficiency leads to chronic granulomatous disease in which those affected are unable to destroy catalase-positive organisms

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(Choice A) Cytochrome oxidase is the final component of the electron transport chain and functions to convert molecular oxygen to water while establishing the proton gradient necessary for synthesis of ATP.

(Choice B) Cytochrome P450 enzymes metabolize endogenous toxins as well as drugs. They are capable of producing reactive oxygen species, which can contribute to the hepatotoxicity seen with certain drugs.

(Choice C) Myeloperoxidase is found in neutrophils and converts hydrogen peroxide to hypochlorous acid, a bactericidal compound that also causes oxidative damage to host cells.

(Choice D) NADPH oxidase catalyzes the reduction of molecular oxygen to superoxide free radicals, aiding in bacterial destruction by phagocytic cells. Deficiency leads to chronic granulomatous disease in which those affected are unable to destroy catalase-positive organisms.

Educational objective:
As an antioxidant, superoxide dismutase neutralizes reactive oxygen species, preventing cell injury. In a pathologic state such as post-ischemic reperfusion, oxidative stress is high and reactive oxygen species production exceeds the neutralizing capability of antioxidants, leading to increased cell damage and death.

References

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A 45-year-old previously healthy man comes to the office for evaluation of a neck lump. The patient first noticed the swelling a month ago while shaving, and it has progressively enlarged. He has had no fever, neck pain, hoarseness, or difficulty breathing or swallowing. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 78/min. On physical examination, there is a nontender, firm nodule in the upper portion of the left thyroid lobe. Laboratory studies reveal a normal serum TSH and elevated serum calcitonin levels. Neck ultrasonography shows a 2-cm hypoechoic thyroid nodule with microcalcifications. Fine-needle aspiration of the nodule reveals spindle-shaped cells in an amorphous background. Which of the following gene alterations most likely contributed to this patient's current condition?

A. Activation of *ALK*
B. Activation of *RET*
C. Inactivation of *MEN1*
D. Inactivation of p53
E. Overexpression of *BCL2*

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A. Activation of *ALK*
B. Activation of *RET*
C. Inactivation of *MEN1*
D. Inactivation of p53
E. Overexpression of *BCL2*
F. Overexpression of *JAK2*

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A. Activation of *ALK* (0%)
B. Activation of *RET* (76%)
C. Inactivation of *MEN1* (16%)
D. Inactivation of p53 (3%)
E. Overexpression of *BCL2* (1%)
F. Overexpression of *JAK2* (0%)

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Tumors associated with specific oncogenes	
Proto-oncogenes (tumor promoters)	
ABL	Chronic myeloid leukemia
ALK	Large cell lymphoma, non–small cell lung cancer
BRAF	Melanoma
HER1	Squamous cell lung cancer
HER2/neu	Breast cancer, ovarian cancer
MYC	Neuroblastoma (NMYC), small cell lung cancer (LMYC)
RET	Medullary thyroid cancer, pheochromocytoma
Anti-oncogenes (tumor suppressors)	
APC/β catenin	Colorectal cancer, pancreatic cancer
BRCA1, BRCA2	Breast cancer, ovarian cancer

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NF1	Neuroblastoma, sarcoma
RB	Retinoblastoma, osteosarcoma
VHL	Renal cell cancer
WT1	Wilms tumor

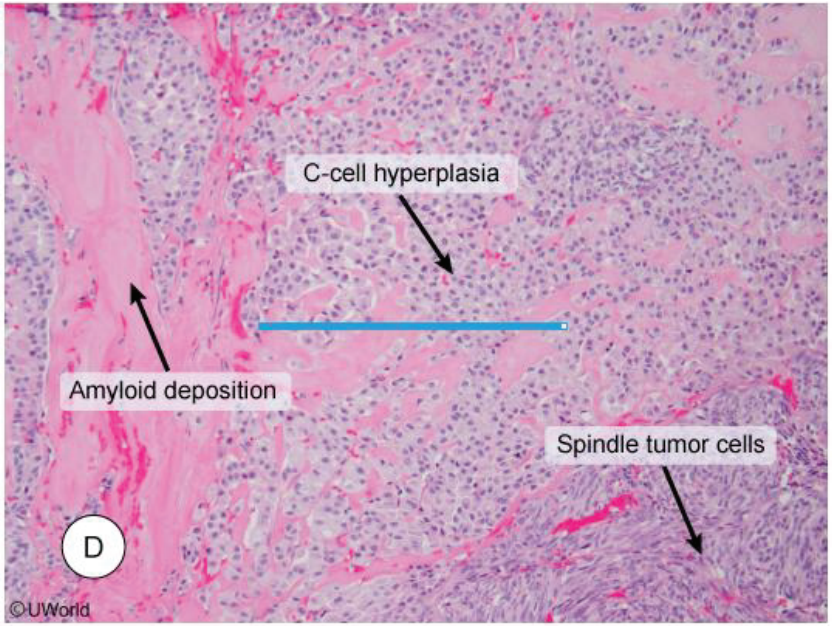
This patient has **medullary thyroid cancer** (MTC) presenting with a palpable nodule and elevated serum calcitonin. MTC is a neuroendocrine tumor that arises from **calcitonin-secreting** C (parafollicular) cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells, often with extracellular amyloid deposition (consisting of full-length calcitonin). MTC is often seen in the context of multiple endocrine neoplasia type 2 (A and B), although the majority of cases are sporadic. Paraneoplastic symptoms (eg, diarrhea, flushing) can occur due to elevated calcitonin levels; however, calcium is usually normal, possibly due to the downregulation of calcitonin receptors.

MTC is associated with activating mutations in the ***RET* proto-oncogene**; mutations are commonly found in sporadic MTC, and germline mutations are present in more than 95% of patients with familial MTC. The *RET* proto-oncogene codes for a membrane-bound **tyrosine kinase receptor** involved in cell cycle regulation. In patients with MTC, **constitutive activation** of the receptor leads to unregulated cellular

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regulation. In patients with MTC, **constitutive activation** of the receptor leads to unregulated cellular proliferation.

(Choice A) The anaplastic lymphoma kinase (*ALK*) oncogene codes for a transmembrane receptor tyrosine kinase. Mutations are common in anaplastic large cell lymphoma and non–small cell lung cancer.

(Choice C) The *MEN1* gene codes for a tumor suppressor protein. Mutations are associated with multiple endocrine neoplasia type 1 (pituitary adenomas, primary hyperparathyroidism, pancreatic neuroendocrine tumors) but not type 2.

(Choice D) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control. Inactivating mutations or deletions are present in a large percentage of human tumors, including anaplastic thyroid cancer, but not typically in early-stage MTC.

(Choice E) *BCL2* (B-cell lymphoma 2) is an antiapoptotic gene that enhances cell survival. Its expression is upregulated in many cancer cells. *BCL2* mutations are common in many follicular lymphomas.

(Choice F) Mutations in *JAK2* (Janus kinase 2) are seen in a variety of myeloproliferative disorders such as primary polycythemia and essential thrombocythemia.

Educational objective:

Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting C (parafollicular)

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tumors) but not type 2.

(Choice D) p53 is a tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle control. Inactivating mutations or deletions are present in a large percentage of human tumors, including anaplastic thyroid cancer, but not typically in early-stage MTC.

(Choice E) *BCL2* (B-cell lymphoma 2) is an antiapoptotic gene that enhances cell survival. Its expression is upregulated in many cancer cells. *BCL2* mutations are common in many follicular lymphomas.

(Choice F) Mutations in *JAK2* (Janus kinase 2) are seen in a variety of myeloproliferative disorders such as primary polycythemia and essential thrombocythemia.

Educational objective:

Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting C (parafollicular) cells. It is often seen in the context of multiple endocrine neoplasia type 2 (A and B), although the majority of cases are sporadic. Both sporadic and familial medullary thyroid cancers are associated with mutations in the *RET* proto-oncogene.

References

- Diversity of mutations in the RET proto-oncogene and its oncogenic mechanism in medullary thyroid

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A 24-year-old man is evaluated for recurrent episodes of abdominal pain and bloody diarrhea. The patient has also had low-grade fevers and fatigue. Physical examination reveals left lower quadrant tenderness. CT scan of the abdomen shows thickening of the distal colon and rectum. During one of the laboratory tests, the patient's anticoagulated blood is placed in an upright, thin glass tube and left undisturbed. His red blood cells form a stack and settle to the bottom at a fast rate of 50 mm/hr. Serum levels of which of the following substances is most closely associated with this observed finding?

A. Bradykinin
B. Erythropoietin
C. Interleukin (IL)-6
D. Leukotriene B_4
E. Platelet-activating factor
F. Thromboxane A_2

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A. Bradykinin (3%)
B. Erythropoietin (7%)
C. Interleukin (IL)-6 (45%)
D. Leukotriene B_4 (4%)
E. Platelet-activating factor (13%)
F. Thromboxane A_2 (25%)

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This patient who has recurrent abdominal pain and bloody diarrhea with CT evidence of bowel wall thickening in the distal colon and rectum likely has ulcerative colitis. Chronic inflammatory conditions are characterized by the persistent stimulation of neutrophils and macrophages, leading to long-term elevation of circulating pro-inflammatory cytokines such as IL-1, **IL-6**, tumor necrosis factor-alpha, and interferon-gamma. The liver responds to these circulating cytokines (particularly IL-6) by generating **acute phase reactants**, proteins that modulate and influence the inflammatory response and play some role in innate immunity.

Testing for acute phase reactants can help diagnose and track conditions associated with inflammation, including infections, autoimmune diseases, and malignancies. The test described in this case is the **erythrocyte sedimentation rate** (ESR), which begins by placing whole blood in a narrow vertical tube. Erythrocytes settle at the bottom of the tube over time due to gravity as their density is greater than plasma. ESR is a measure of the length of plasma on top of the erythrocyte sediment layer at 1 hour. The presence of acute phase reactants, particularly fibrinogen and globulins, causes erythrocytes to overcome their zeta potential (negative charge that separates them) and form a stacked, **rouleaux formation**, which settles to the bottom of the tube more quickly and **increases ESR**.

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(Choice A) Bradykinin is a component of the kinin system. It is a short-lived peptide that causes vasodilation, increases vascular permeability, stimulates endothelial smooth muscle dilation, and mediates pain.

(Choice B) Erythropoietin is a growth factor for erythrocyte precursors in the bone marrow. It is produced by peritubular cells of the kidneys in response to hypoxia.

(Choice D) Leukotriene B_4 is a metabolite of arachidonic acid. Its main function is to stimulate neutrophil migration to the site of inflammation.

(Choice E) Platelet-activating factor is released by endothelium, platelets, and immune cells, and is involved in leukocyte function (eg, endothelium attachment, phagocytosis, degranulation), platelet stimulation, and changes to vascular tone and permeability.

(Choice F) Thromboxane A_2 is one of the products of the cyclooxygenase pathway. It is synthesized by platelets and causes platelet activation and aggregation. It does not cause erythrocyte aggregation or rouleaux formation.

Educational objective:
Chronic inflammation is associated with increased circulating pro-inflammatory cytokines (eg, IL-1, IL-6,

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(Choice F) Thromboxane A_2 is one of the products of the cyclooxygenase pathway. It is synthesized by platelets and causes platelet activation and aggregation. It does not cause erythrocyte aggregation or rouleaux formation.

Educational objective:

Chronic inflammation is associated with increased circulating pro-inflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha), which stimulates the liver to release acute-phase reactants (eg, C-reactive protein, fibrinogen). The presence of acute-phase reactants increases the erythrocyte sedimentation rate, a nonspecific marker for inflammation.

References

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A 46-year-old Caucasian male presents to your office with a slowly growing neck mass. The mass is stony hard on palpation and seems to be fixed to the adjacent tissues. After initial evaluation, combination chemotherapy is prescribed to the patient. Several weeks later the mass significantly decreases in size, and biopsy demonstrates many shrunken eosinophilic cells within the tumor. Which of the following substances released from mitochondria most likely triggered the observed cellular changes?

A. Hemosiderin
B. Fas (CD95)
C. Cytochrome c
D. Succinate dehydrogenase
E. Superoxide dismutase
F. Lipoxygenase

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A 46-year-old Caucasian male presents to your office with a slowly growing neck mass. The mass is stony hard on palpation and seems to be fixed to the adjacent tissues. After initial evaluation, combination chemotherapy is prescribed to the patient. Several weeks later the mass significantly decreases in size, and biopsy demonstrates many shrunken eosinophilic cells within the tumor. Which of the following substances released from mitochondria most likely triggered the observed cellular changes?

A. Hemosiderin (1%)
B. Fas (CD95) (11%)
C. Cytochrome c (68%)
D. Succinate dehydrogenase (2%)
E. Superoxide dismutase (11%)
F. Lipoxygenase (3%)

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Correct answer

68%
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Apoptosis is a means of carefully regulated cell death in which the cell activates enzymes to degrade its own nuclear DNA and proteins. Although the cell membrane remains intact during apoptosis, the cell becomes an appealing target for phagocytosis. Because no cell contents are leaked into the surrounding tissue, there is no associated inflammation.

The process of apoptosis is separated into an initiation phase and an execution phase. During the initiation phase, protein-hydrolyzing caspases are activated. In the execution phase, these caspases bring about the cell death by cleaving cellular proteins and activating DNAses.

The initiation of apoptosis occurs via signals from two separate pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway. In the intrinsic pathway, the mitochondria become more permeable and pro-apoptotic substances are released into the cytoplasm in response to stress or the cessation of survival signals. Once the cell is exposed to stress or the cessation of survival signals, the anti-apoptotic proteins Bcl-2 and Bcl-x that reside in the mitochondrial membranes and cytoplasm are replaced with pro-apoptotic proteins such as Bak, Bax, and Bim. The pro-apoptotic proteins allow for the increased permeability of the mitochondria, which results in the release of caspase-activating substances like cytochrome c.

(Choice A) Hemosiderin accumulation is common in patients who have hemolytic anemia or who undergo

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(Choice A) Hemosiderin accumulation is common in patients who have hemolytic anemia or who undergo frequent blood transfusions. It is not associated with apoptosis.

(Choice B) The extrinsic pathway requires engagement of death receptors on the cell surface. These death receptors are in the tumor necrosis factor receptor family, with the type 1 TNF receptor (TNFR1) and a related protein named Fas (CD95) the two best known members of this family. After cross-linkage of Fas with its ligand, multiple molecules of Fas come together to form a binding site for a death-domain containing adapter protein called FADD. FADD then binds an inactive form of a caspase, again bringing multiple caspase proteins together that through a cascade effect eventually induce caspase activation.

(Choice D) Succinate dehydrogenase is a mitochondrial enzyme in the electron transport chain that acts by oxidizing succinate into fumarate and reducing FAD to $FADH_2$. This enzyme is not involved in apoptosis.

(Choice E) Superoxide dismutase catalyzes the reduction of superoxide anions to hydrogen peroxide. This enzyme is not involved in apoptosis.

(Choice F) Lipoxygenase plays a key role in the synthesis of leukotrienes, a class of inflammatory mediators.

Educational Objective:

Cytochrome c is a mitochondrial enzyme that activates caspases and indirectly brings about cell death

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containing adapter protein called FADD. FADD then binds an inactive form of a caspase, again bringing multiple caspase proteins together that through a cascade effect eventually induce caspase activation.

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(Choice E) Superoxide dismutase catalyzes the reduction of superoxide anions to hydrogen peroxide. This enzyme is not involved in apoptosis.

(Choice F) Lipoxygenase plays a key role in the synthesis of leukotrienes, a class of inflammatory mediators.

Educational Objective:
Cytochrome c is a mitochondrial enzyme that activates caspases and indirectly brings about cell death through intrinsic pathway apoptosis.

Pathology	Pathology (General Principles)	Apoptosis
Subject	System	Topic

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A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9 F). Examination shows nasal and pharyngeal hyperemia. Rapid influenza antigen testing of nasopharyngeal secretions is positive. Within the infected cells of the patient's respiratory tract, viral proteins are degraded and attached to major histocompatibility complex class I molecules, which are then expressed on the cell surface for presentation to cytotoxic $CD8^+$ lymphocytes. Which of the following enzymes is most essential to initiating this process?

A. Acid phosphatase
B. Caspase
C. Guanylate cyclase
D. Myeloperoxidase
E. Ubiquitin ligase

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A 26-year-old man comes to the office due to myalgia, nasal congestion, and cough. Temperature is 38.3 C (100.9 F). Examination shows nasal and pharyngeal hyperemia. Rapid influenza antigen testing of nasopharyngeal secretions is positive. Within the infected cells of the patient's respiratory tract, viral proteins are degraded and attached to major histocompatibility complex class I molecules, which are then expressed on the cell surface for presentation to cytotoxic $CD8^+$ lymphocytes. Which of the following enzymes is most essential to initiating this process?

- A. Acid phosphatase (14%)
- B. Caspase (20%)
- C. Guanylate cyclase (5%)
- D. Myeloperoxidase (13%)
- ✓ E. Ubiquitin ligase (46%)

Correct

46%
Answered correctly

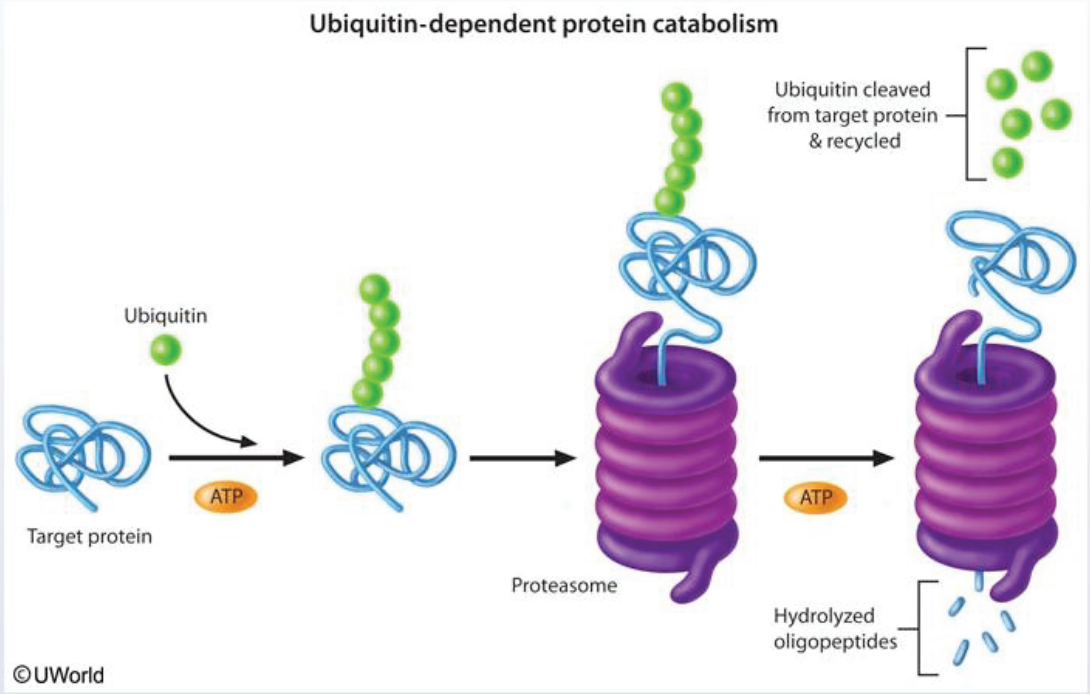
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Explanation



The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens

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The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens to effector immune cells (eg, $CD8^+$ lymphocytes). The **ubiquitin proteasome pathway** (UPP) is essential to this process because of its role in breaking down native and foreign intracellular proteins. **Ubiquitin ligase** initiates the UPP by recognizing specific protein substrates and catalyzing the attachment of ubiquitin. The proteins tagged with ubiquitin are then **broken down** by a proteasome to peptide fragments which can be recycled into amino acids.

The **peptide fragments** produced during this process can also be coupled to major histocompatibility complex (MHC) class I molecules in the endoplasmic reticulum and then presented on the cell surface. **Cytotoxic $CD8^+$ lymphocytes** recognize nonnative (eg, viral) proteins on infected cells and trigger **apoptosis** of the cell by activating the caspase cascade through the release perforin and granzyme **(Choice B)**.

(Choice A) Acid phosphatase is found in the lysosome of most cells and hydrolyzes organic phosphates, but it is not involved in antigen presentation.

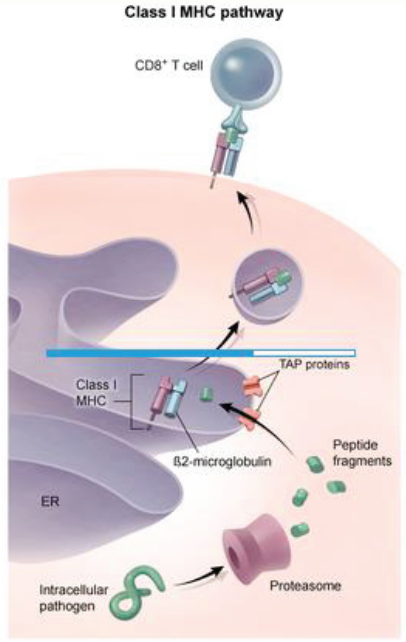
(Choice C) Guanylate cyclase is involved in the G-protein signaling cascade, which plays a crucial role in the activation and regulation of diverse physiologic processes (eg, smooth muscle relaxation, retinal phototransduction).

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The cellular immune response to a viral pathogen (eg, influenza) requires the presentation of viral antigens

Exhibit Display



ER = endoplasmic reticulum; MHC = major histocompatibility complex; TAP = transporter associated with antigen processing.

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but it is not involved in antigen presentation.

(Choice C) Guanylate cyclase is involved in the G-protein signaling cascade, which plays a crucial role in the activation and regulation of diverse physiologic processes (eg, smooth muscle relaxation, retinal phototransduction).

(Choice D) Myeloperoxidase is a key component of the respiratory burst of neutrophils and is released into the phagocytic vacuole and extracellular space as part of the immune response to bacteria and other pathogens.

Educational objective:

An essential step in the activation of the cellular immune response to a virus is the breakdown of intracellular viral proteins by the ubiquitin proteasome pathway. This pathway is initiated by ubiquitin ligases, which recognize specific protein substrates and attach a ubiquitin tag. The target proteins are then degraded by a proteasome into peptide fragments, which are coupled with major histocompatibility complex class I proteins and presented on the cell surface for surveillance by cytotoxic $CD8^+$ lymphocytes.

References

- The ubiquitin-proteasome system and its role in inflammatory and autoimmune diseases.

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A 50-year-old woman comes to the office for an annual examination. She is healthy and takes no medications other than vitamin D and calcium supplements. The patient does not smoke, drink alcohol, or use illicit drugs. Her blood pressure is 118/69 mm Hg. Physical examination is unremarkable. A recent mammogram was normal. A colonoscopy showed 2 polyps, which were excised. On histological examination, one polyp is small and has early adenoma features; the other is larger and has late adenoma features. A mutation in which of the following genes would most likely cause this patient's small early adenoma to grow and develop late adenoma features?

- A. *BRCA1*
- B. *CCND1*
- C. *KRAS*
- D. *NMYC*
- E. *TP53*
- F. *WT1*

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- A. *BRCA1* (1%)
- B. *CCND1* (2%)
- ✓ C. *KRAS* (75%)
- D. *NMYC* (2%)
- E. *TP53* (16%)
- F. *WT1* (0%)

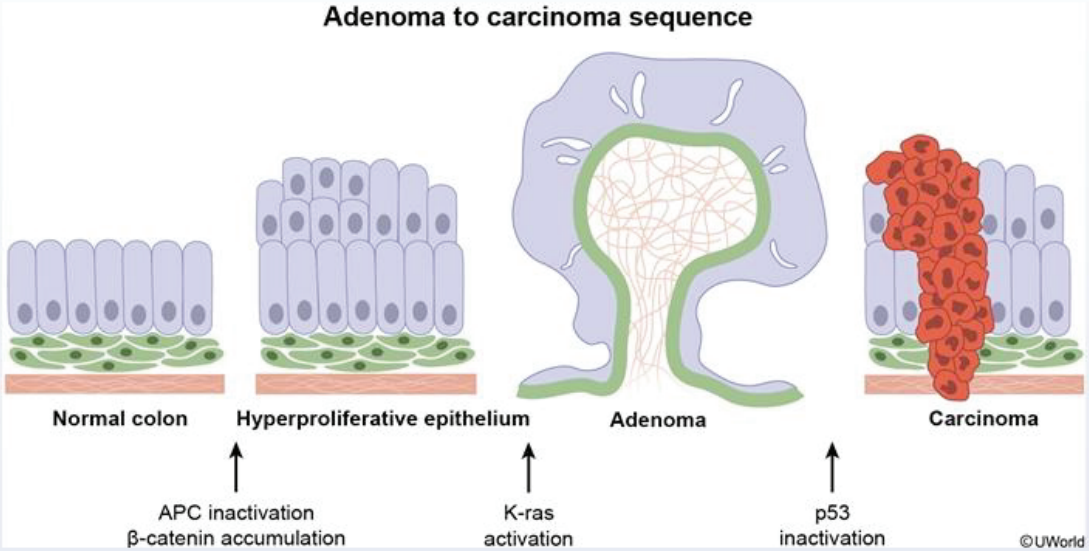
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75%

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Most colon adenocarcinomas develop from preexisting adenomatous polyps (adenomas). **Colon adenomas** usually occur in patients in their 50s and 60s and are considered **premalignant**. On average, 10 years are required for malignant transformation of adenoma; therefore, early detection and excision of adenomatous polyps can help prevent colon adenocarcinoma. Features that impact the malignant potential of adenomatous polyps include **size** (<1 cm, unlikely to undergo malignant transformation; >4 cm,

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10 years are required for malignant transformation of adenoma; therefore, early detection and excision of adenomatous polyps can help prevent colon adenocarcinoma. Features that impact the malignant potential of adenomatous polyps include **size** (<1 cm, unlikely to undergo malignant transformation; >4 cm, 40% risk of malignancy), histologic appearance (**villous** more prone to malignant transformation than tubular), and degree of dysplasia.

Transformation of normal mucosal cells into malignant ones is caused by a series of gene mutations called the **adenoma to carcinoma sequence**:

1. **Progression from normal mucosa to a small adenomatous polyp (adenoma)**. The initial appearance of small adenomatous polyps is attributed to mutation of the *APC* tumor suppressor gene.
2. **Increase in the size of the adenoma**. Mutation of the *KRAS* protooncogene is thought to facilitate this step (going from a small early to a large late adenoma, as with this patient) by leading to **uncontrolled cell proliferation**. Normally, *KRAS* encodes for a G protein-like protein that regulates the cell cycle by stimulating and inhibiting it as necessary. Mutation of *KRAS* into its oncogene form leads to a constitutively activated GTP-bound protein.
3. **Malignant transformation** of adenoma into carcinoma. This step requires mutation of ***TP53***, a tumor suppressor gene that regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely in adenomas **(Choice E)**.

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3. **Malignant transformation** of adenoma into carcinoma. This step requires mutation of *TP53*, a tumor suppressor gene that regulates the cell cycle and promotes repair of damaged DNA; mutations are found in most colon carcinomas but rarely in adenomas **(Choice E)**.

(Choice A) Mutations in the tumor suppressor gene *BRCA* are classically associated with breast and ovarian cancers.

(Choice B) Cyclin D is a protein (encoded by *CCND1*) that regulates cell cycle. Its overexpression is seen in breast, lung, and esophageal cancers and certain types of lymphomas.

(Choice D) An increased number of copies (amplification) of the *NMYC* oncogene are seen in neuroblastoma.

(Choice F) Mutation of *WT1*, a tumor suppressor gene, leads to the development of Wilms tumor.

Educational objective:
The size of adenomatous polyps determines their malignant potential. Adenomas <1 cm are unlikely to undergo malignant transformation, whereas those >4 cm are very likely to progress to adenocarcinoma. *KRAS* protooncogene mutation facilitates the growth of adenomas by causing uncontrolled cell proliferation.

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A 72-year-old man comes to the office due to progressive weakness, fatigue, anorexia, and a 10-kg (22-lb) weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

A. Calcium channel autoantibody
B. Interferon-α
C. Interleukin-3
D. Transforming growth factor-β
E. Tumor necrosis factor-α
F. Vasopressin

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weight loss over the past 4 months. He says that food doesn't taste as good as it once did, and he feels full after eating only a small amount. The patient has had a morning cough for the past several years and had streaks of blood in his sputum 2 weeks ago. He has a 50-pack-year smoking history. On examination, the patient appears frail with a sunken face and bitemporal wasting. His arms are thin with notable muscle wasting. Lung examination reveals wheezing on the right side. Chest x-ray reveals an irregular right perihilar mass. Which of the following is most likely contributing to this patient's muscle wasting?

A. Calcium channel autoantibody (13%)
B. Interferon-α (5%)
C. Interleukin-3 (1%)
D. Transforming growth factor-β (6%)
E. Tumor necrosis factor-α (71%)
F. Vasopressin (1%)

Correct

71%
Answered correctly

13 secs
Time Spent

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Cachexia is a syndrome that encompasses anorexia, malaise, anemia, weight loss, and generalized **wasting** due to underlying systemic disease. Cachexia in this patient is likely a manifestation of the lung **neoplasm** revealed on his chest x-ray. **Tumor necrosis factor-α** (TNF-α) is a cytokine that causes necrosis of some tumors in vitro and produces symptoms of cachexia in experimental animals. TNF-α is also called cachectin and is considered a main mediator of paraneoplastic cachexia (along with interleukin [IL]-1β, and IL-6).

TNF-α is produced by macrophages in response to infection as well as by some neoplastic cells. Its role in cachexia is explained by its influence on the hypothalamus, leading to appetite suppression. It also increases basal metabolic rate. In bacterial infections, TNF-α produces fever (along with IL-1), mediates many of the symptoms of septic shock, and causes hepatic release of acute-phase reactants (eg, C-reactive protein and fibrinogen).

(Choice A) Eaton-Lambert syndrome is a paraneoplastic condition that manifests as progressive, symmetric proximal muscle weakness (rather than wasting) along with ocular and autonomic symptoms. It is due to autoantibodies to voltage-gated calcium channels.

(Choice B) Interferon-α is synthesized by leukocytes and has antiviral as well as anti-tumor activity.

(Choice C) IL-3 is produced by activated CD4+ T cells. It stimulates growth and differentiation of myeloid

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is due to autoantibodies to voltage-gated calcium channels.

(Choice B) Interferon-α is synthesized by leukocytes and has antiviral as well as anti-tumor activity.

(Choice C) IL-3 is produced by activated CD4+ T_H cells. It stimulates growth and differentiation of myeloid cells.

(Choice D) The main function of transforming growth factor-β is inhibition of the inflammatory response. It decreases T cell proliferation and cytokine production.

(Choice F) Production of vasopressin by some tumors (eg, small cell lung cancer) results in the syndrome of inappropriate antidiuretic hormone secretion.

Educational objective:
Tumor necrosis factor-α is thought to mediate paraneoplastic cachexia in humans by suppressing appetite and increasing basal metabolic rate.

Pathology	Pathology (General Principles)	Cancer anorexia cachexia syndrome
Subject	System	Topic

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A 45-year-old woman comes to the office due to 2 weeks of persistent back pain. She has also had excessive fatigue, anorexia, and unintentional weight loss over the past several months. The patient has no prior medical problems but has a history of cancer in the family. An imaging study reveals a lytic lesion in the T10 vertebral body. Analysis of the biopsy sample shows cell lineage with abnormally high replicative potential. A genetic study reveals a single nucleotide substitution causing an activating mutation. Which of the following genes is most likely involved in this patient's disease?

A. *APC*
B. *BRCA1*
C. *KRAS*
D. *RB*
E. *TP53*

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- ✗ A. *APC* (7%)
- B. *BRCA1* (18%)
- ✓ C. *KRAS* (45%)
- D. *RB* (13%)
- E. *TP53* (15%)

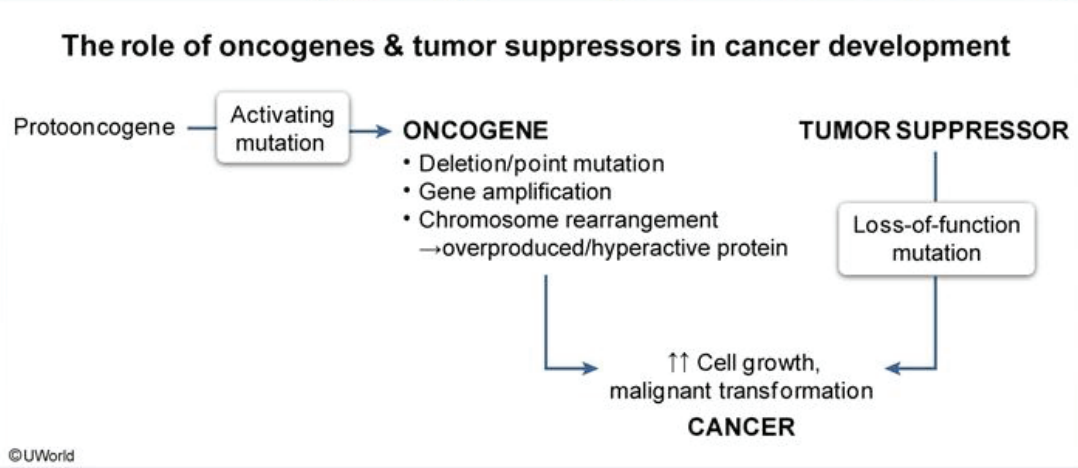
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Correct answer
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45%
Answered correctly

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Abnormal growth of neoplastic cells can arise due to mutation of either proto-oncogenes or anti-oncogenes (tumor suppressors). **Proto-oncogenes** stimulate cell proliferation, and their overexpression/amplification (eg, **activating** mutation) leads to increased cellular proliferation and neoplastic growth. ***KRAS*** is a proto-oncogene often activated in tumor cells, thereby increasing the cellular response to mitogenic stimuli.

In contrast, anti-oncogenes are **tumor suppressors** as they inhibit cellular proliferation. Their inactivation (eg, **loss-of-function** mutation) contributes to tumor development. *APC, BRCA1, RB*, and *TP53* are anti-oncogenes and are therefore more likely to be inactivated in neoplastic cells:

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oncogenes and are therefore more likely to be inactivated in neoplastic cells:

- *APC* is inactivated in familial adenomatous polyposis syndrome. Similar mutations are found in many sporadic colon cancers **(Choice A)**
- *BRCA1* is responsible for DNA repair. Its inactivation increases the risk of developing breast and ovarian cancer **(Choice B)**
- When active, *RB* suppresses the transition of cells from the G1 to S phase of the cell cycle, thereby inhibiting cellular proliferation. An inactivated *RB* is found in many tumors **(Choice D)**
- Mutated *TP53* is the most common abnormality associated with cancer development. *TP53* is a tumor suppressor gene that produces p53, a protein that inhibits proliferation of cells with genetic abnormalities **(Choice E)**

Some of the important proto-oncogenes, anti-oncogenes, and their associated tumors are listed in the table.

Educational objective:
Most tumors possess multiple cytogenetic abnormalities. Activation of proto-oncogenes results in stimulation of cellular proliferation. Inactivation of anti-oncogenes eliminates oversight of the cell cycle.

Pathology Pathology (General Principles) Colorectal polyps and cancer

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oncogenes and are therefore more likely to be inactivated in neoplastic cells:

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Proto-oncogenes/tumor promoters	Anti-oncogenes/tumor suppressors
• *ABL:* Chronic myeloid leukemia, acute lymphoblastic leukemia	• *APC*/β-catenin: Stomach cancer, colon cancer, pancreatic cancer, familial adenomatous polyposis
• *BRAF:* Melanoma	• *BRCA1, BRCA2:* Breast cancer, ovarian cancer
• *HER1:* Squamous cell lung cancer	• *DCC:* Colon cancer
• *HER2:* Breast cancer, ovarian cancer	• *NF1:* Neuroblastoma, neurofibromatosis type 1, sarcoma
• *MYC:* Neuroblastoma (*NMYC*); small cell lung cancer (*LMYC*)	• *RB:* Retinoblastoma, osteosarcoma, other cancers
• *RAS:* Lung cancer, colon cancer, pancreatic cancer (*KRAS*); renal cell cancer, bladder cancer (*HRAS*)	• *TP53:* Most cancers, Li-Fraumeni syndrome
• *SIS:* Astrocytoma, osteosarcoma	• *VHL:* Von Hippel-Lindau syndrome, renal cell cancer
• *TGFA:* Astrocytoma, hepatocellular carcinoma	• *WT1:* Wilms tumor

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Pathology | Pathology (General Principles) | Colorectal polyps and cancer

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A researcher studying the cell cycle observes a sudden increase in the activity of several enzymes, including dihydrofolate reductase and DNA polymerase. Which of the following processes most immediately precedes the observed increase in enzyme activity?

A. Caspase enzyme cleavage
B. GDP binding to Ras protein
C. p27 protein upregulation
D. Protein kinase A phosphorylation
E. Retinoblastoma protein phosphorylation

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A researcher studying the cell cycle observes a sudden increase in the activity of several enzymes, including dihydrofolate reductase and DNA polymerase. Which of the following processes most immediately precedes the observed increase in enzyme activity?

A. Caspase enzyme cleavage (3%)
B. GDP binding to Ras protein (15%)
C. p27 protein upregulation (7%)
D. Protein kinase A phosphorylation (16%)
E. Retinoblastoma protein phosphorylation (57%)

Correct

57% Answered correctly

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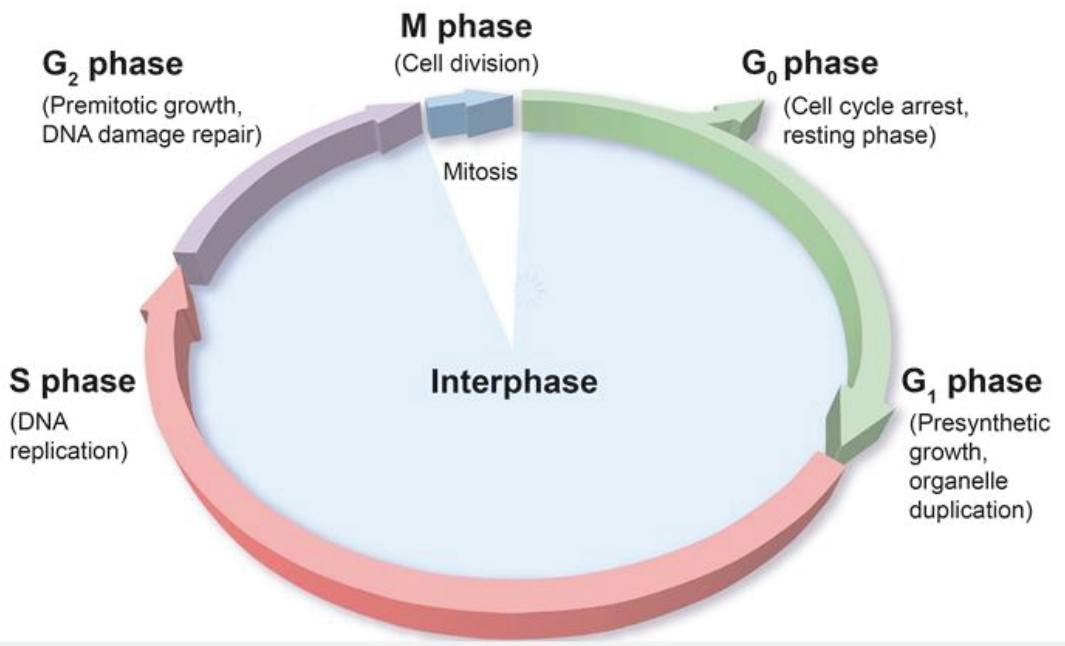
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Explanation

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the G1/S checkpoint, in which the cell ensures DNA integrity. Cells with damaged DNA are not allowed to

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An increase in the activity of enzymes responsible for **DNA synthesis** (eg, dihydrofolate reductase, DNA polymerase) signifies that the cell is in the **S phase** of the cell cycle. **Immediately prior** to the S phase is the **G1/S checkpoint**, in which the cell ensures DNA integrity. Cells with damaged DNA are not allowed to enter the S phase to limit propagation of mutations.

Retinoblastoma (Rb) protein is a regulator of the G1/S phase transition. The Rb protein has two forms, active (dephosphorylated) or inactive (phosphorylated). When the cell is stimulated by growth factors, activation of cyclin D, cyclin E, and the corresponding cyclin kinases (CDK 4 and 2) occurs and the Rb protein is **phosphorylated** (rendering it inactive). Phosphorylated Rb releases the E2F transcription factor, which **allows progression through the G1/S checkpoint**. After the cell divides, Rb protein is dephosphorylated (active) and remains so until the cell is ready to enter S phase again.

In terminally differentiated cells, the Rb protein stays in the dephosphorylated (active) state bound to E2F transcription factors, resulting in inhibited transcription of genes necessary for G1/S transition. Therefore, active Rb protein stops the cell from dividing and allows the cell to enter a quiescent (G0) phase.

(Choice A) Caspases are cysteine proteases, enzymes essential for apoptosis. Caspases are not associated with the G1/S transition in the cell cycle.

(Choice B) Ras protein is a component of the MAP-kinase signal transduction system. It transmits growth

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(Choice A) Caspases are cysteine proteases, enzymes essential for apoptosis. Caspases are not associated with the G1/S transition in the cell cycle.

(Choice B) Ras protein is a component of the MAP-kinase signal transduction system. It transmits growth signals from cell surface receptors into the nucleus, leading to the transcription of cyclin D complexes. Although involved in cell cycle progression, Ras protein signaling would occur before phosphorylation of RB protein and would not immediately precede the S phase.

(Choice C) The p27 protein is a cell cycle inhibitor. It acts during the G1 phase by inhibiting cyclin-dependent kinases. Normal tissues (composed primarily of differentiated cells) contain high levels of p27, and malignant tissues contain very low levels of p27. Upregulation of p27 would stop the cell cycle.

(Choice D) Protein kinase A is a component of the cAMP signaling system. It is not associated with the G1/S transition in the cell cycle.

Educational objective:
Dihydrofolate reductase and DNA polymerase are enzymes involved in DNA synthesis, which occurs during the S phase of the cell cycle. The Rb protein, in its active (dephosphorylated) form, regulates cell cycle progression by preventing the transition from the G1 phase to the S phase. Phosphorylation of the Rb protein inactivates it, allowing cells to progress through the G1/S checkpoint and proliferate.

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A 54-year-old male presents with an enlarged left-sided supraclavicular lymph node. The node is painless and stony hard on palpation. The node biopsy reveals anaplastic cells that stain positive for keratin. Which of the following is the most likely origin of the cells detected on the biopsy?

A. Lymphocytes
B. Epithelial surfaces
C. Muscle tissue
D. Endothelium
E. Glial cells

Submit

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A 54-year-old male presents with an enlarged left-sided supraclavicular lymph node. The node is painless and stony hard on palpation. The node biopsy reveals anaplastic cells that stain positive for keratin. Which of the following is the most likely origin of the cells detected on the biopsy?

- A. Lymphocytes (2%)
- ✓ B. Epithelial surfaces (88%)
- C. Muscle tissue (1%)
- D. Endothelium (5%)
- E. Glial cells (1%)

Correct

88% Answered correctly

25 secs Time Spent

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Explanation

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Keratins are a broad group of intermediate filaments present in epithelial cells. Immunohistochemistry stains that employ keratin markers are used by pathologists in the identification of poorly differentiated tumors or tumors with an unclear site of origin. Tumors that stain positive for keratin include carcinomas, mesotheliomas, thymomas, various sarcomas, trophoblastic tumors, and desmoplastic small round cell tumors.

(Choice A) Lymphocytes can be identified immunohistochemically with a special stain for the pan T cell marker CD3, among others.

(Choice C) Muscle tissue can be identified immunohistochemically with special stains for smooth muscle actin, caldesmon, or desmin, among others.

(Choice D) Endothelium can be identified immunohistochemically with special stains for CD34 and von Willebrand's factor, among others.

(Choice E) Glial cells can be identified immunohistochemically with a special stain for glial fibrillary acidic protein.

Educational Objective:

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tumors.

(Choice A) Lymphocytes can be identified immunohistochemically with a special stain for the pan T cell marker CD3, among others.

(Choice C) Muscle tissue can be identified immunohistochemically with special stains for smooth muscle actin, caldesmon, or desmin, among others.

(Choice D) Endothelium can be identified immunohistochemically with special stains for CD34 and von Willebrand's factor, among others.

(Choice E) Glial cells can be identified immunohistochemically with a special stain for glial fibrillary acidic protein.

Educational Objective:
Keratin is a marker of epithelial cell origin.

Pathology	Pathology (General Principles)	Immunohistochemistry
Subject	System	Topic

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A 62-year-old woman comes to the physician after finding a lump in her breast. Physical examination reveals a firm, immovable, irregularly shaped mass. Mammography is performed and shows a spiculated, calcified lesion that was not seen on prior studies. A tissue biopsy is diagnostic for infiltrating ductal carcinoma. Malignant tumors such as infiltrating ductal carcinoma are typically associated with varying degrees of disordered differentiation and maturation. Which of the following findings is most characteristic of an anaplastic tumor?

A. Brain tumor cells forming giant cells
B. Bronchial epithelial cells producing keratin pearls
C. Colonic tumor cells creating glands
D. Hepatic tumor cells synthesizing bile
E. Skin tumor cells producing keratin pearls

Submit

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A 62-year-old woman comes to the physician after finding a lump in her breast. Physical examination reveals a firm, immovable, irregularly shaped mass. Mammography is performed and shows a spiculated, calcified lesion that was not seen on prior studies. A tissue biopsy is diagnostic for infiltrating ductal carcinoma. Malignant tumors such as infiltrating ductal carcinoma are typically associated with varying degrees of disordered differentiation and maturation. Which of the following findings is most characteristic of an anaplastic tumor?

- A. Brain tumor cells forming giant cells (49%)
- B. Bronchial epithelial cells producing keratin pearls (31%)
- C. Colonic tumor cells creating glands (7%)
- D. Hepatic tumor cells synthesizing bile (3%)
- E. Skin tumor cells producing keratin pearls (8%)

Correct

49% Answered correctly

01 min, 19 secs Time Spent

12/02/2020 Last Updated

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Well differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally similar to normal cells in the tissue of origin. In contrast, poorly differentiated (high-grade) tumors contain neoplastic cells that lack most of the characteristic features of the original tissue. Neoplasms that contain cells in the midst of this spectrum are termed moderately differentiated (medium-grade). Neoplastic cells that demonstrate a complete lack of differentiation are termed anaplastic.

Anaplastic tumors typically demonstrate the following features:

1. Loss of cell polarity with complete disruption of normal tissue architecture; cells coalesce into sheets or islands in a disorganized, infiltrative fashion (example, compare to normal)
2. Significant variation in the shape and size of cells (cellular pleomorphism) and nuclei (nuclear pleomorphism)
3. Disproportionately large nuclei (high nucleus-to-cytoplasm ratio) that are often deep-staining (hyperchromatic) with abundant, coarsely-clumped chromatin and large nucleoli (example)
4. Numerous, often abnormal, mitotic figures
5. Giant, multinucleated tumor cells**(Choice A)**

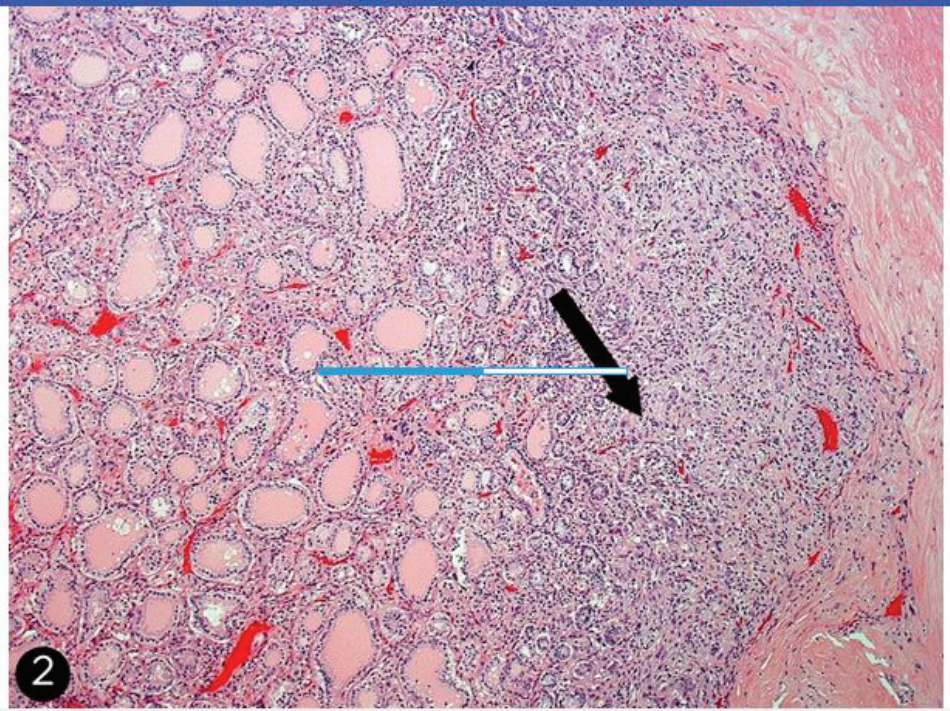
(Choices B and E) The production of keratin pearls by skin tumor cells is an example of dysplasia (ie, disordered growth). The fact that they produce keratin means that the tumor cells are well differentiated.

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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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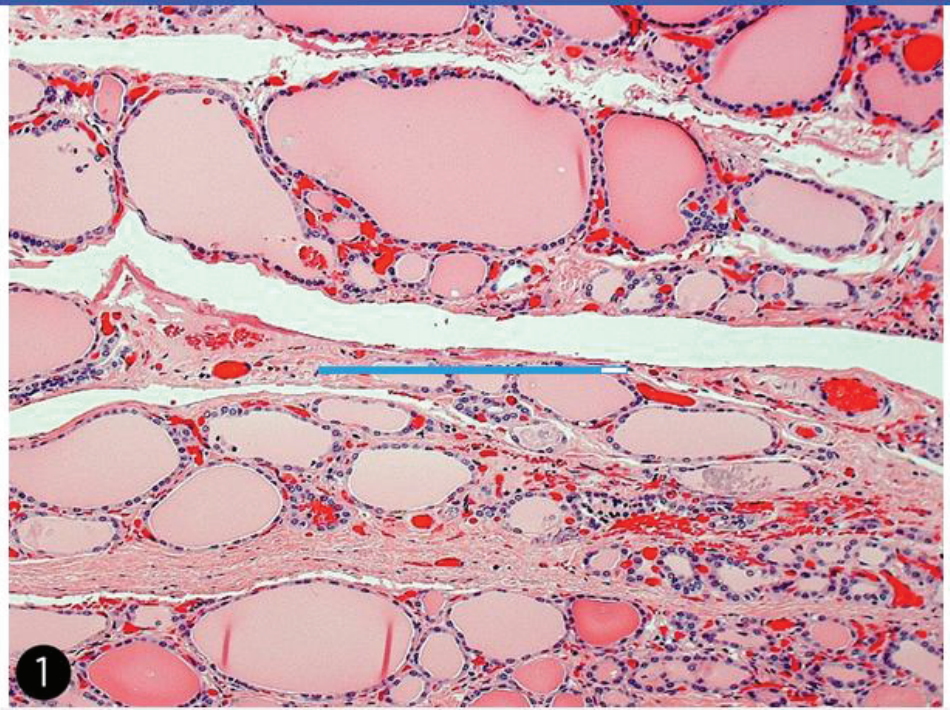
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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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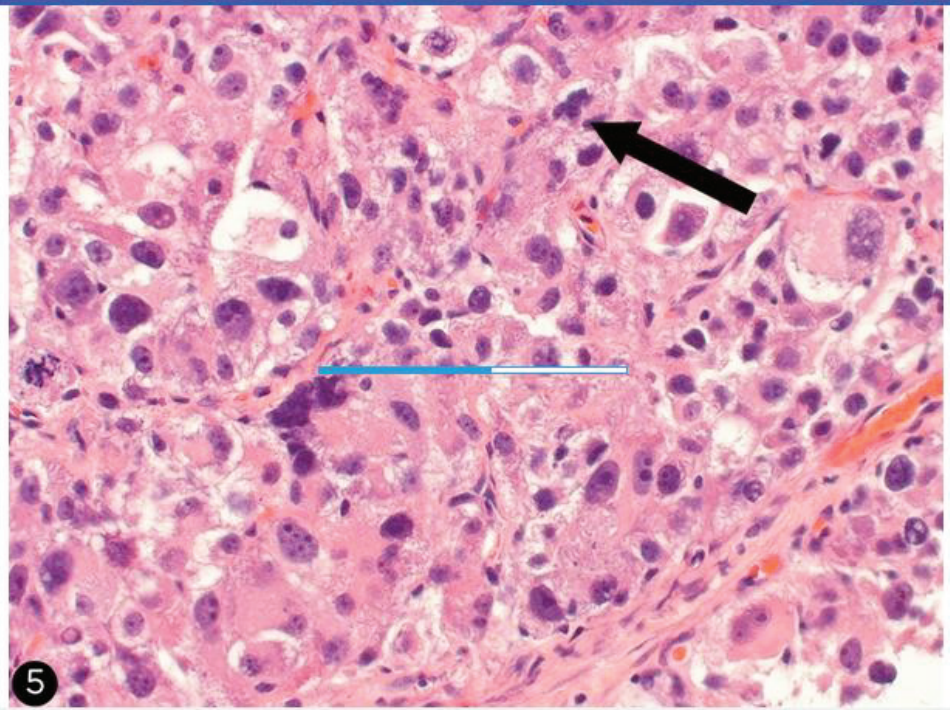
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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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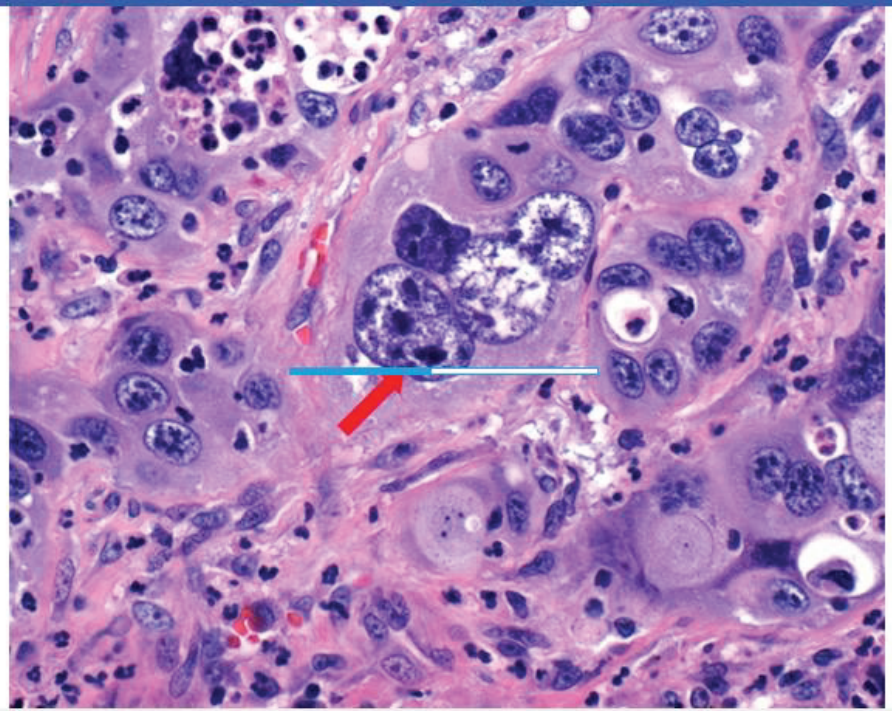
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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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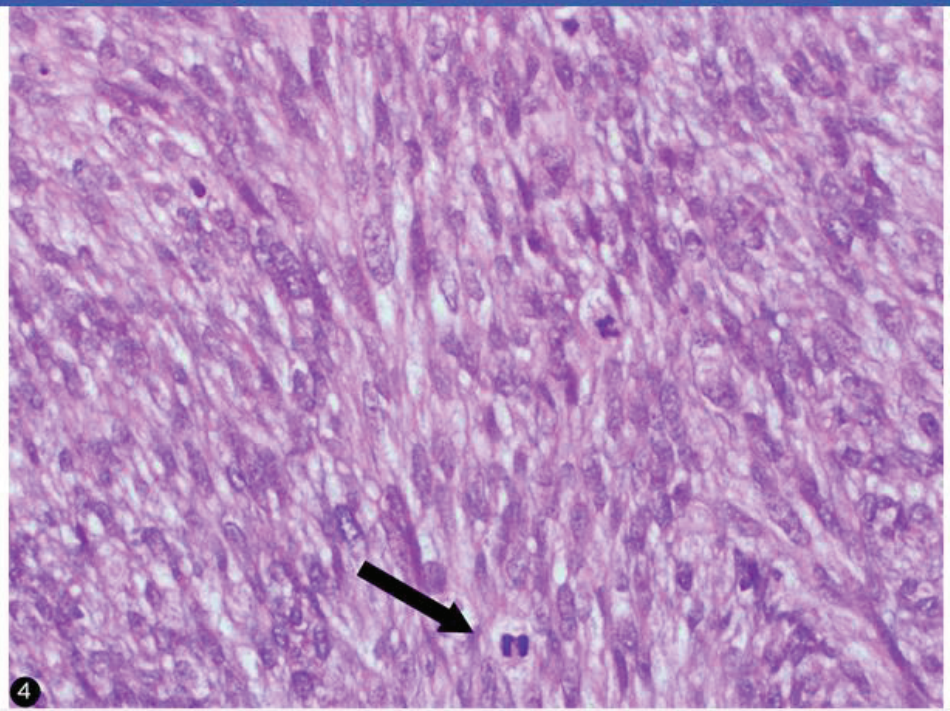
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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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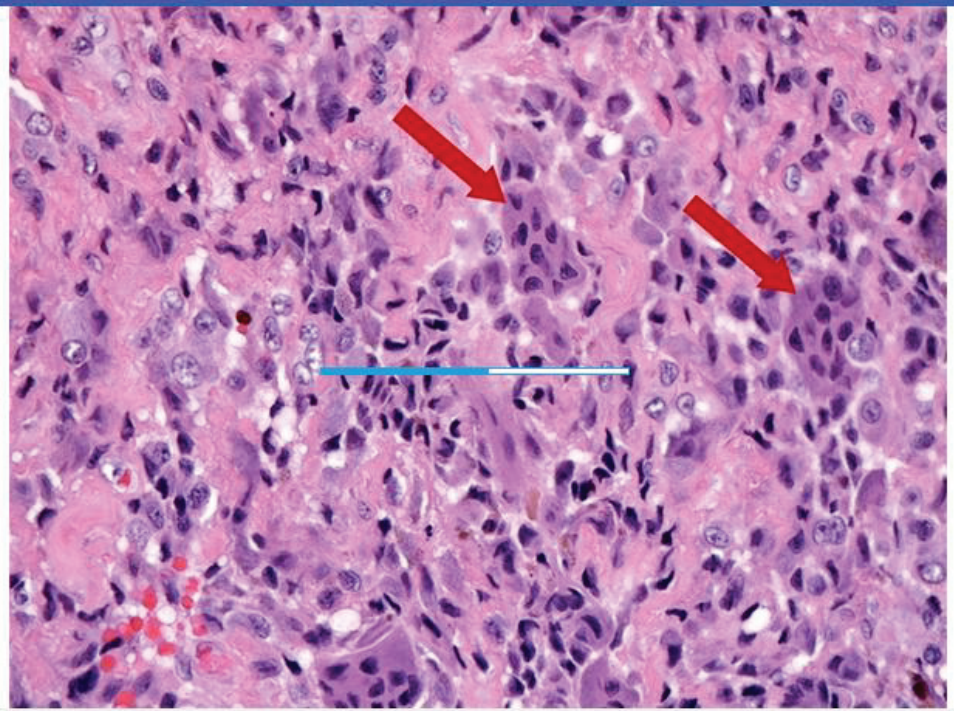
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Well-differentiated (low-grade) tumors contain neoplastic cells that are morphologically and architecturally

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(Choices B and E) The production of keratin pearls by skin tumor cells is an example of dysplasia (ie, disordered growth). The fact that they produce keratin means that the tumor cells are well differentiated. Bronchial epithelial cells can also produce keratin pearls after undergoing a phenotypic switch from columnar epithelium to squamous epithelium. The process of switching from one differentiated cell type to another is known as metaplasia and often occurs in response to irritants (eg, tobacco smoke or gastric acid).

(Choices C and D) Cells in the colon normally form goblet cell-containing glands and cells in hepatic tissue normally synthesize bile. Therefore, the described tumor cells would be well-differentiated, not anaplastic.

Educational objective:
Undifferentiated (anaplastic) tumors bear no resemblance to the tissue of origin. They are composed of pleomorphic cells with large, hyperchromatic nuclei that grow in a disorganized fashion. Anaplastic tumors may also contain numerous, abnormal mitoses and giant tumor cells.

Pathology	Pathology (General Principles)	Breast cancer
Subject	System	Topic

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A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

- A. Acid hydrolase
- B. Alkaline phosphatase
- C. Carboxypeptidase
- D. E-cadherin
- E. Hyaluronic acid
- F. Metalloproteinase

Submit

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A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

- A. Acid hydrolase (3%)
- B. Alkaline phosphatase (3%)
- C. Carboxypeptidase (2%)
- ✗ D. E-cadherin (19%)
- E. Hyaluronic acid (4%)
- ✓ F. Metalloproteinase (66%)

Incorrect
Correct answer

66%
Answered correctly

35 secs
Time Spent

01/25/2021
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Metalloproteinases are zinc-containing enzymes that degrade components of the extracellular matrix (ECM) and basement membrane, which are composed primarily of laminin and collagens IV and VII. These enzymes participate in many physiologic processes, such as tissue remodeling and embryogenesis. They also facilitate **basement membrane penetration**, which distinguishes an invasive tumor from carcinoma in situ and includes the following steps:

1. Tumor cells **detach** from surrounding cells in a process commonly determined by decreased (rather than increased) expression of adhesion molecules, including **E-cadherins (Choice D)**
2. Tumor cells **adhere** to the basement membrane; this is facilitated by increased expression of **laminin** and other adhesion molecules
3. Tumor cells **invade** the basement membrane via enhanced secretion of **proteolytic enzymes** (eg, **metalloproteinases**, cathepsin D protease)

(Choice A) Acid hydrolases, which function at acidic pH, are primarily degradative lysosomal enzymes.

(Choice B) In humans, alkaline phosphatase is concentrated in liver cells; elevated levels suggest an obstructive biliary process.

(Choice C) Carboxypeptidases cleave peptide bonds at the carboxy-terminal; some participate in the synthesis of insulin and neuropeptides

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3. Tumor cells **invade** the basement membrane via enhanced secretion of **proteolytic enzymes** (eg, **metalloproteinases**, cathepsin D protease)

(Choice A) Acid hydrolases, which function at acidic pH, are primarily degradative lysosomal enzymes.

(Choice B) In humans, alkaline phosphatase is concentrated in liver cells; elevated levels suggest an obstructive biliary process.

(Choice C) Carboxypeptidases cleave peptide bonds at the carboxy-terminal; some participate in the synthesis of insulin and neuropeptides.

(Choice E) Hyaluronic acid is an ECM component.

Educational objective:
Metalloproteinases are zinc-containing enzymes that degrade the extracellular matrix. They participate in normal tissue remodeling and in tumor invasion through the basement membrane and connective tissue.

Pathology	Pathology (General Principles)	Matrix metalloprotease
Subject	System	Topic

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A 4-year-old girl is brought to the clinic due to an inward deviated right eye. Examination shows a pale red reflex in the right eye relative to the left eye. Dilated funduscopic examination reveals a well-circumscribed white mass within the retina. Genetic analysis shows a germline mutation in the patient's cells leading to development of the mass. Which of the following is the most likely function of the protein affected by this patient's gene mutation?

A. Activation of receptor tyrosine kinase
B. Conversion of GTP to GDP
C. Opposition of p53 activity
D. Prevention of the G1/S cell cycle transition
E. Repair of damaged DNA

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A. Activation of receptor tyrosine kinase (2%)
B. Conversion of GTP to GDP (1%)
C. Opposition of p53 activity (6%)
✓ D. Prevention of the G1/S cell cycle transition (85%)
E. Repair of damaged DNA (3%)

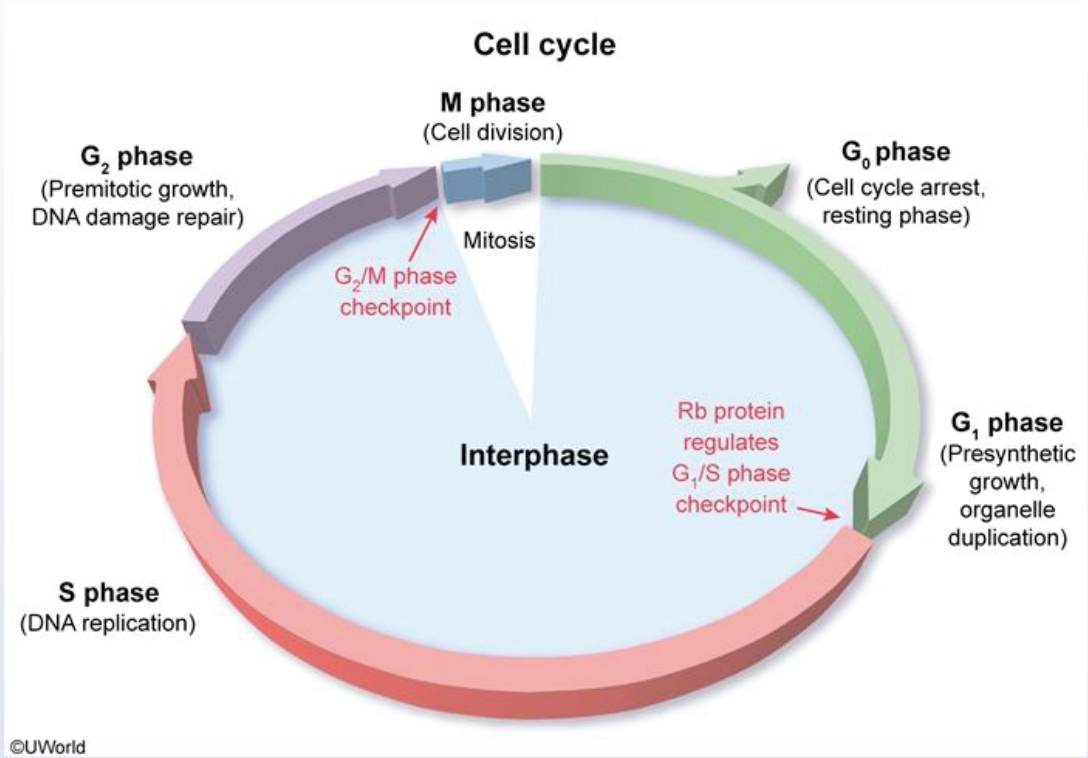
Correct

85%
Answered correctly

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This patient's pale red reflex and well-circumscribed white mass within the retina are indicative of

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This patient's pale red reflex and well-circumscribed white mass within the retina are indicative of **retinoblastoma**. Retinoblastoma is an intraocular tumor caused by inactivating mutations affecting the ***RB1*tumor suppressor gene** with subsequent dysregulation of the cell cycle.

The cell cycle consists of the following stages:

- Gap phase 0 (G0 phase) is a resting stage in which the cell cycle is suspended.
- Interphase is the stage in which the cell prepares for division. Interphase is subdivided into the G1 phase (synthesis of RNA, protein, lipid, and carbohydrate), S phase (DNA replication), and the G2 phase (ATP synthesis).
- Mitosis (M) is the stage in which the cell divides into two daughter cells.

Checkpoints occur at the G1/S and G2/M transitions, allowing the cell cycle to be stopped if damaged DNA is detected by cyclins and cyclin-dependent kinases. DNA repair mechanisms are activated, but if the DNA damage is too substantial, the cell undergoes apoptosis.

The ***RB1* gene** encodes the Rb protein that regulates the **G1/S checkpoint**. In its active form, Rb protein binds and inhibits E2F transcription factors, thereby halting the cell cycle. In contrast, when a cell is ready to divide, Rb protein is phosphorylated by cyclin-dependent kinases, allowing the cell to proceed through

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(Choice A) Many receptor tyrosine kinases have stimulatory effects on cell growth, and increased receptor activity occurs with a variety of cancers. For example, overexpression of *EGFR* and *MET* are associated with non–small cell lung cancer, and *HER2* is associated with breast cancer.

(Choice B) Abnormal K-Ras GTPase function due to a *KRAS* mutation prevents the conversion of GTP to GDP, which results in constant activation of the MAPK pathway and uncontrolled cellular proliferation. *KRAS* mutations are associated with lung and colorectal cancers, not retinoblastoma.

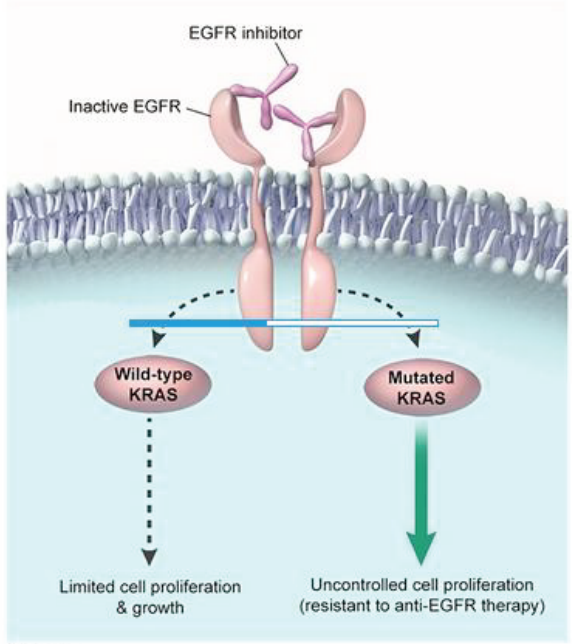
(Choice C) Tumor suppressor protein p53 arrests the cell cycle at the G1/S checkpoint if DNA damage is detected and initiates cell apoptosis if DNA repair fails. Mutations of p53 are associated with most cancers, particularly Li-Fraumeni syndrome (sarcoma, breast, leukemia, and adrenal cancers). Rb and p53 proteins are both critical components of tumor suppression pathways, and their normal function complements one another to prevent cancer progression.

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The ***RB1* gene** encodes the Rb protein that regulates the **G1/S checkpoint**. In its active form, Rb protein

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KRAS mutation causing anti-EGFR resistance



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(Choice E) *BRCA1* and *BRCA2* are two of many DNA repair genes that have been identified. When mutated, these genes are associated with an increased risk of breast and ovarian cancer.

Educational objective:

Retinoblastoma is associated with inactivating mutations of the *RB1* tumor suppressor gene, which normally restricts cells from passing the G1/S checkpoint until the cell is ready to divide. Impaired function of the Rb protein allows unrestricted progression through the G1/S checkpoint, leading to uncontrolled cell division.

References

- Molecular mechanisms underlying RB protein function.

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A 64-year-old man develops diarrhea, abdominal pain, nausea, vomiting, and anorexia 3 weeks after starting radiation therapy for prostate cancer. Physical examination shows abdominal tenderness. Sigmoidoscopy reveals hyperemia, edema, erosion, and ulceration of the intestinal mucosa. Stool and serum chemistries are normal. Radiation enteritis is suspected. Which of the following is most likely the primary mechanism responsible for this patient's intestinal changes?

- A. Generation of reactive oxygen species
- B. Increased activity of the ubiquitin-proteasome system
- C. Inhibition of DNA polymerase
- D. Inhibition of thymidylate synthesis
- E. Prevention of microtubule assembly

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- A. Generation of reactive oxygen species (69%)
- B. Increased activity of the ubiquitin-proteasome system (10%)
- C. Inhibition of DNA polymerase (8%)
- D. Inhibition of thymidylate synthesis (7%)
- E. Prevention of microtubule assembly (4%)

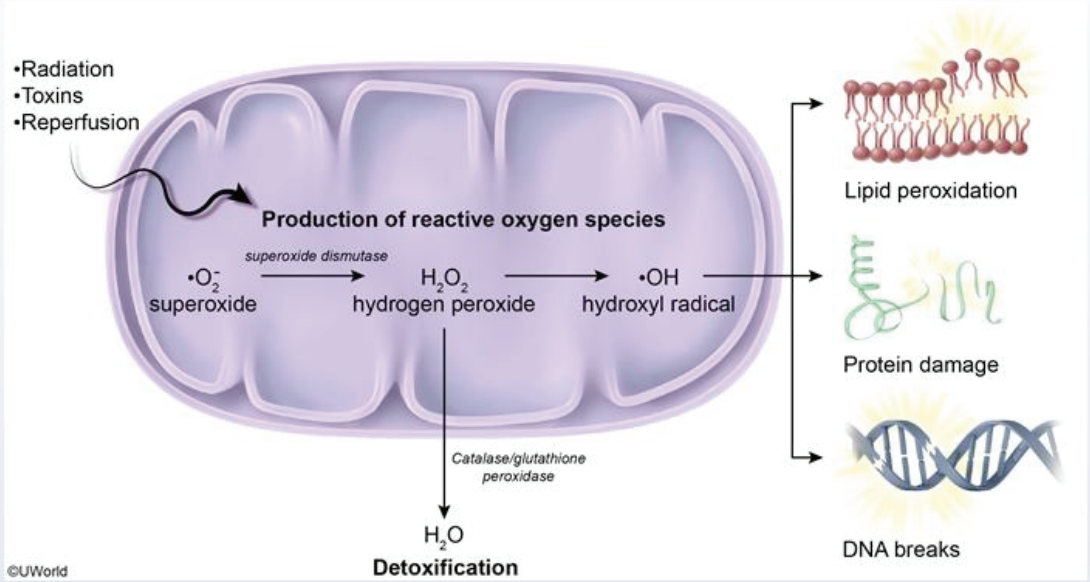
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69% Answered correctly

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This patient developed signs of **acute radiation enteritis** (eg, abdominal pain, diarrhea, inflammation and denudation of intestinal mucosa) 3 weeks after starting radiotherapy for **prostate cancer**. Therapeutic **ionizing radiation** is commonly used to treat or palliate many types of cancer (eg, prostate, breast) and causes cell damage through 2 primary mechanisms:

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causes cell damage through 2 primary mechanisms:

- DNA double-strand breakage: Breakage of both strands is required; single-strand breaks can be repaired by polymerases.
- **Generation of reactive oxygen species**: Unstable molecules formed by the ionization of water; oxygen free radicals can cause cellular and DNA damage.

Radiation-induced DNA damage impairs mitosis and initiates **apoptosis** of susceptible cells, including **intestinal crypt stem cells** and other highly proliferative cells (eg, cancer cells, hematogenous precursors). Cellular damage also induces an immune response characterized by increased expression of **proinflammatory cytokines** (eg, IL-1, IL-6, tumor necrosis factor-alpha) and migration of leukocytes (eg, neutrophils) to the affected tissue, processes that produce additional reactive oxygen species and contribute to the radiation-induced tissue damage.

In the gastrointestinal tract, these changes result in progressive inflammation, edema, and **mucosal denudation** that decrease the absorptive area. Abdominal pain and diarrhea typically manifest several weeks after radiotherapy is started. In some cases, the effects of radiation exposure can be delayed until years after radiation exposure and present as complications of intestinal fibrosis (eg, strictures, adhesions, bowel obstruction).

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bowel obstruction).

(Choice B) The ubiquitin-proteasome system has an integral role in maintaining normal cell function by degrading damaged proteins and contributing to cell cycle control. Although proteasome activity normally increases in response to oxidative stress, this system is inhibited by ionizing radiation, potentiating the apoptotic effects of radiotherapy.

(Choices C, D, and E) Many chemotherapeutic agents impair essential steps in the DNA and cellular repair processes and can potentiate the effects of ionizing radiation. Although inhibition of DNA polymerase (eg, nucleoside analogues), inhibition of thymidylate synthesis (eg, 5-fluorouracil), and prevention of microtubule assembly (eg, vinblastine) would contribute to the cytotoxic effects of radiation, radiation-induced tissue damage occurs primarily through the generation of free radicals.

Educational objective:
Ionizing radiation causes cellular and DNA damage primarily through generation of reactive oxygen species, which can trigger progressive inflammation and tissue damage. In the gastrointestinal tract, the acute effects of radiation exposure typically occur several weeks after radiotherapy is initiated and manifest as abdominal pain and diarrhea due to mucosal denudation, inflammation, and edema.

References

- Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials

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